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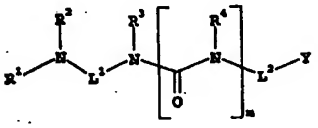
(54) Title: SUBSTITUTED DIAMINES AND THEIR USE AS CELL ADHESION INHIBITORS

(57) Abstract

The invention is directed to physiologically active compounds of general formula (I): wherein $R^1$ represents $R^5$–$L^3$–, $R^5$–$L^4$–$R^6$–, $R^5$–$L^4$–$R^7$–$L^5$–, $R^5$–$L^4$–$Ar^1$–$L^3$–, $R^5$–$L^4$–$Ar^1$–$L^6$–$R^6$– or $R^5$–$L^4$–$Ar^1$–$R^7$–$L^5$–; $R^2$ represents hydrogen or lower alkyl; $R^3$ and $R^4$ independently represent hydrogen or a group selected from alkyl, alkenyl and alkynyl each optionally substituted by one or more atoms or groups chosen from halo, oxo $R^8$, –C(=O)–$R^9$, –NH–C(=O)–$R^9$, or –C(=O)$NY^1Y^2$; or $R^3$ and $R^4$ together may represent $–(CH_2)_n–$ or C(=O)–CH=CH–; $L^1$ represents $C_{2-6}$alkylene or formula (II); or the group $–L^1–N(R^3)–$ represents formula (III); or the group $–N(R^2)–L^1–$ represents formula (IV); or the group $–N(R^2)–L^1–N(R^3)–$ represents formula (V); $L^2$ represents an alkylene, alkenylene, alkynylene, cycloalkenylene, cycloalkylene or heterocycloalkylene linkage, each optionally substituted by alkyl, alkenyl, alkynyl, aryl, carboxy (or an acid bioisostere), cyano, cycloalkenyl, cycloalkyl, heteroaryl, heterocycloalkyl, oxo, –C(=O)$R^9$, –C(=O)$OR^9$, –C(=O)$NY^1Y^2$ or $–NY^1Y^2$, or by alkyl substituted by aryl, carboxy (or an acid bioisostere), cyano, heteroaryl, heterocycloalkyl, hydroxy, mercapto, –C(=O)$R^9$, –C(=O)$OR^9$, –C(=O)$NY^1Y^2$, $–OR^9$, $S(O)_vR^9$, –NHC(=O)Oalkyl, $–NY^1Y^2$, $–NR^{10}C(=Z)–NY^3Y^4$ or –NH–C(=NH)$NH_2$; or the group $–N(R^4)–L^2–$ represents formula (VI); Y is carboxy (or an acid bioisostere) or –C(=O)–$NY^1Y^2$; and m is zero or 1; and their prodrugs, and pharmaceutically acceptable salts and solvates of such compounds and their prodrugs. Such compounds have valuable pharmaceutical properties, in particular the ability to regulate the interaction of VCAM-1 and fibronectin with the integrin VLA-4($\alpha 4\beta 1$).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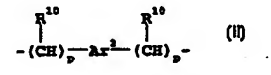
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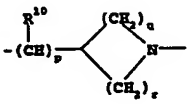
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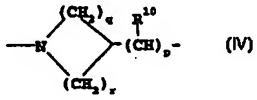
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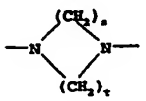
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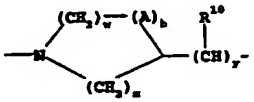
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# SUBSTITUTED DIAMINES AND THEIR USE AS CELL ADHESION INHIBITORS

This invention is directed to substituted diamines, their preparation, pharmaceutical compositions containing these compounds, and their pharmaceutical use in the treatment of disease states capable of being modulated by the inhibition of cell adhesion.

Cell adhesion is a process by which cells associate with each other, migrate towards a specific target or localise within the extra-cellular matrix. Many of the cell-cell and cell-extracellular matrix interactions are mediated by protein ligands (e.g. fibronectin, VCAM-1 and vitronectin) and their integrin receptors [e.g. $\alpha 5\beta 1$ (VLA-5), $\alpha 4\beta 1$ (VLA-4) and $\alpha V\beta 3$]. Recent studies have shown these interactions to play an important part in many physiological (e.g. embryonic development and wound healing) and pathological conditions (e.g. tumour-cell invasion and metastasis, inflammation, atherosclerosis and autoimmune disease).

A wide variety of proteins serve as ligands for integrin receptors. In general, the proteins recognised by integrins fall into one of three classes: extracellular matrix proteins, plasma proteins and cell surface proteins. Extracellular matrix proteins such as collagen fibronectin, fibrinogen, laminin, thrombospondin and vitronectin bind to a number of integrins. Many of the adhesive proteins also circulate in plasma and bind to activated blood cells. Additional components in plasma that are ligands for integrins include fibrinogen and factor X. Cell bound complement C3bi and several transmembrane proteins, such as Ig-like cell adhesion molecule (ICAM-1,2,3) and vascular cell adhesion molecule (VCAM-1), which are members of the Ig superfamily, also serve as cell-surface ligands for some integrins.

Integrins are heterodimeric cell surface receptors consisting of two subunits called $\alpha$ and $\beta$. There are at least fifteen different $\alpha$-subunits ($\alpha 1$-$\alpha 9$, $\alpha$-L, $\alpha$-M, $\alpha$-X, $\alpha$-IIb, $\alpha$-V and $\alpha$-E) and at least seven different $\beta$ ($\beta 1$-$\beta 7$) subunits. The integrin family can be subdivided into classes based on the $\beta$ subunits, which can be associated with one or more $\alpha$-subunits. The most widely distributed integrins belong to the $\beta 1$ class, also known as the very late antigens (VLA). The second class of integrins are leukocyte specific receptors and consist of one of three $\alpha$-subunits ($\alpha$-L, $\alpha$-M or $\alpha$-X) complexed with the $\beta 2$ protein. The cytoadhesins $\alpha$-IIb$\beta 3$ and $\alpha$-V$\beta 3$, constitute the third class of integrins.

The present invention principally relates to agents which modulate the interaction of the ligand VCAM-1 with its integrin receptor α4β1 (VLA-4), which is expressed on numerous hematopoietic cells and established cell lines, including hematopoietic precursors, peripheral and cytotoxic T lymphocytes, B lymphocytes, monocytes, thymocytes and eosinophils.

The integrin α4β1 mediates both cell-cell and cell-matrix interactions. Cells expressing α4β1 bind to the carboxy-terminal cell binding domain (CS-1) of the extracellular matrix protein fibronectin, to the cytokine-inducible endothelial cell surface protein VCAM-1, and to each other to promote homotypic aggregation. The expression of VCAM-1 by endothelial cells is upregulated by proinflammatory cytokines such as INF-γ, TNF-α, IL-1β and IL-4.

Regulation of α4β1 mediated cell adhesion is important in numerous physiological processes, including T-cell proliferation, B-cell localisation to germinal centres, and adhesion of activated T-cells and eosinophils to endothelial cells. Evidence for the involvement of VLA-4/VCAM-1 interaction in various disease processes such as melanoma cell division in metastasis, T-cell infiltration of synovial membranes in rheumatoid arthritis, autoimmune diabetes, collitis and leukocyte penetration of the blood-brain barrier in experimental autoimmune encephalomyelitis, atherosclerosis, peripheral vascular disease, cardiovascular disease and multiple sclerosis, has been accumulated by investigating the role of the peptide CS-1 (the variable region of fibronectin to which α4β1 binds via the sequence Leu-Asp-Val) and antibodies specific for VLA-4 or VCAM-1 in various in vitro and in vivo experimental models of inflammation. For example, in a Streptococcal cell wall-induced experimental model of arthritis in rats, intravenous administration of CS-1 at the initiation of arthritis suppresses both acute and chronic inflammation (S.M.Wahl et al., J.Clin.Invest., 1994, 94, pages 655-662). In the oxazalone-sensitised model of inflammation (contact hypersensitivity response) in mice, intravenous administration of anti-α4 specific monoclonal antibodies significantly inhibited (50-60% reduction in the ear swelling response) the efferent response (P.L.Chisholm et al. J.Immunol., 1993, 23, pages 682-688). In a sheep model of allergic bronchoconstriction, HP1/2, an anti-α4 monoclonal antibody given intravenously or by aerosol, blocked the late response and the development of airway hyperresponsiveness (W.M. Abraham et al. J. Clin. Invest., 1994, 93 pages 776-787).

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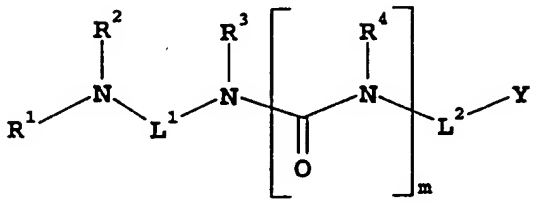
We have now found a novel group of substituted diamines which have valuable pharmaceutical properties, in particular the ability to regulate the interaction of VCAM-1 and fibronectin with the integrin VLA-4 (α4β1).

Thus, in one aspect, the present invention is directed to compounds of general formula (I):-



(I)

wherein:-

$R^1$ represents a group selected from :

(i) $R^5$-$L^3$-

(ii) $R^5$-$L^4$-$R^6$-

(iii) $R^5$-$L^4$-$R^7$-$L^5$-

(iv) $R^5$-$L^4$-$Ar^1$-$L^3$-

(v) $R^5$-$L^4$-$Ar^1$-$L^6$-$R^6$-

(vi) $R^5$-$L^4$-$Ar^1$-$R^7$-$L^5$-

$R^2$ represents hydrogen or lower alkyl;

$R^3$ and $R^4$ independently represent hydrogen or a group selected from alkyl, alkenyl and alkynyl each optionally substituted by one or more atoms or groups chosen from halo, oxo, $R^8$, -C(=O)-$R^9$, -NH-C(=O)-$R^9$ or -C(=O)$NY^1Y^2$; or

$R^3$ and $R^4$ together may represent -$(CH_2)_n$- or -C(=O)-CH=CH-;

$R^5$ is alkyl, alkenyl, alkynyl, aryl, arylalkyl, arylalkenyl, arylalkynyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkenyl, cycloalkylalkynyl, cycloalkenyl, cycloalkenylalkyl, heteroaryl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, heterocycloalkyl or heterocycloalkylalkyl;

$R^6$ is an alkylene chain;

$R^7$ is an alkylene chain, an alkenylene chain, or an alkynylene chain;

$R^8$ is an acidic functional group (or corresponding protected derivative), aryl, cycloalkyl, cycloalkenyl, heteroaryl, heterocycloalkyl, -$ZR^9$ or -$NY^1Y^2$;

$R^9$ is alkyl, aryl, arylalkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl or heterocycloalkylalkyl;

$R^{10}$ is a hydrogen atom or a lower alkyl group;

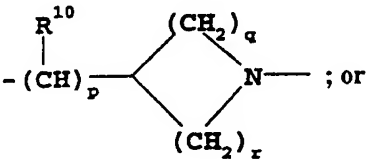
R is hydrogen or $R^9$;

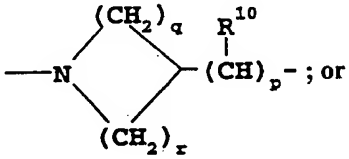
A is -N(R)- or -NH-C(=O)- ;

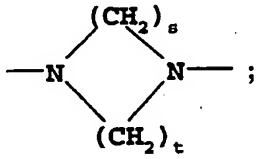
$Ar^1$ is phenylene or heteroaryldiyl;

$Ar^2$ is phenylene, cycloalkylene, heterocycloalkylene or heteroaryldiyl;

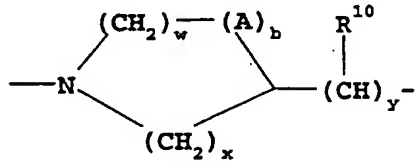
$L^1$ represents $C_{2-6}$alkylene or  ; or

the group $-L^1-N(R^3)-$ represents  ; or

the group $-N(R^2)-L^1-$ represents  ; or

the group $-N(R^2)-L^1-N(R^3)-$ represents  ;

$L^2$ represents an alkylene, alkenylene, alkynylene, cycloalkenylene, cycloalkylene or heterocycloalkylene linkage, each optionally substituted by alkyl, alkenyl, alkynyl, aryl, carboxy (or an acid bioisostere), cyano, cycloalkenyl, cycloalkyl, heteroaryl, heterocycloalkyl, oxo, $-C(=O)R^9$, $-C(=O)OR^9$, $-C(=O)NY^1Y^2$ or $-NY^1Y^2$, or by alkyl substituted by aryl, carboxy (or an acid bioisostere), cyano, heteroaryl, heterocycloalkyl, hydroxy, mercapto, $-C(=O)R^9$, $-C(=O)OR^9$, $-C(=O)NY^1Y^2$, $-OR^9$, $S(O)_vR^9$, -NHC(=O)OAlkyl, $-NY^1Y^2$, $-NR^{10}C(=Z)-NY^3Y^4$ or -NH-C(=NH)$NH_2$; or

the group $-N(R^4)-L^2-$ represents  ;

$L^3$ is a direct bond or a $-C(=Z)-$, $-NR^{10}-C(=Z)-$, -O-C(=O)-, -SO- or $-SO_2-$ linkage;

$L^4$ represents a heteroaryldiyl, heterocycloalkylene, $-NR^{10}-C(=Z)-NR^{10}-$, $-C(=Z)-NR^{10}-$, $-C(=Z)-O-$, $-NR^{10}-C(=Z)-$, -Z-, -SO-, $-SO_2-$, $-NR^{10}-$, $-SO_2-NR^{10}-$, $-NR^{10}-SO_2-$, $-NR^{10}-C(=O)-O-$, -O-C(=O)-, or $-O-C(=O)-NR^{10}-$ linkage;

$L^5$ represents a -C(=Z)-, -$NR^{10}$-C(=Z)-, -O-C(=O)-, -SO- or -$SO_2$- linkage;

$L^6$ is a direct bond, an alkenylene or alkynylene chain, or a -Z-, -SO-, -$SO_2$-, -$NR^{10}$- linkage;

Y is carboxy (or an acid bioisostere) or -C(=O)-$NY^1Y^2$;

$Y^1$ and $Y^2$ are independently hydrogen, acyl, alkyl [optionally substituted by hydroxy, heterocycloalkyl, or one or more carboxy or -C(=O)-$NHR^9$ groups], alkylsulphonyl, aryl, arylalkyloxycarbonyl, arylsulphonyl, arylalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl or heterocycloalkylalkyl; or the group -$NY^1Y^2$ may form a 5-7 membered cyclic amine which (i) may be optionally substituted with one or more substituents selected from carboxamido, carboxy, hydroxy, oxo, hydroxyalkyl, $HOCH_2CH_2$-$(OCH_2CH_2)_v$-, or alkyl optionally substituted by carboxy or carboxamido (ii) may also contain a further heteroatom selected from O, S, $SO_2$ or $NY^5$ and (iii) may also be fused to additional aryl, heteroaryl, heterocycloalkyl or cycloalkyl rings to form a bicyclic or tricyclic ring system;

$Y^3$ and $Y^4$ are independently hydrogen, alkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl or heterocycloalkylalkyl;

$Y^5$ is hydrogen, alkyl, aryl, arylalkyl, -C(=Z)$R^9$ or -$SO_2R^9$;

Z represents an oxygen or sulphur atom;

b is zero or when w is at least 1 then b may also represent 1;

m is zero or 1;

n is an integer 2 to 4;

p is zero or an integer 1 to 3;

q is zero or an integer 1 to 4;

r is an integer 2 to 5; and

q+r is 2 to 7;

s is an integer 1 to 3;

t is an integer 2 or 3; and

s+t is 3 or 5;

v is 0, 1 or 2;

w is zero or an integer 1 to 3;

x is an integer 1 to 3; and

b+w+x is 1 to 5;

y is zero or an integer 1 to 3;

and their prodrugs, and pharmaceutically acceptable salts and solvates (e.g. hydrates) of such compounds and their prodrugs.

In the present specification, the term "compounds of the invention", and equivalent expressions, are meant to embrace compounds of general formula (I) as hereinbefore described, which expression includes the prodrugs, the pharmaceutically acceptable salts, and the solvates, e.g. hydrates, where the context so permits. Similarly, reference to intermediates, whether or not they themselves are claimed, is meant to embrace their salts, and solvates, where the context so permits. For the sake of clarity, particular instances when the context so permits are sometimes indicated in the text, but these instances are purely illustrative and it is not intended to exclude other instances when the context so permits.

As used above, and throughout the description of the invention, the following terms, unless otherwise indicated, shall be understood to have the following meanings:-

"Patient" includes both human and other mammals.

"Acid bioisostere" means a group which has chemical and physical similarities producing broadly similar biological properties to a carboxy group (see Lipinski, Annual Reports in Medicinal Chemistry, 1986,21,p283 "Bioisosterism In Drug Design"; Yun, Hwahak Sekye, 1993,33,p576-579 "Application Of Bioisosterism To New Drug Design"; Zhao, Huaxue Tongbao, 1995,p34-38 "Bioisosteric Replacement And Development Of Lead Compounds In Drug Design"; Graham, Theochem, 1995,343,p105-109 "Theoretical Studies Applied To Drug Design:ab initio Electronic Distributions In Bioisosteres"). Examples of suitable acid bioisosteres include: -C(=O)-NHOH, -C(=O)-$CH_2$OH, -C(=O)-$CH_2$SH, -C(=O)-NH-CN, sulpho, phosphono, alkylsulphonylcarbamoyl, tetrazolyl, arylsulphonylcarbamoyl, heteroarylsulphonylcarbamoyl, N-methoxycarbamoyl, 3-hydroxy-3-cyclobutene-1,2-dione, 3,5-dioxo-1,2,4-oxadiazolidinyl or heterocyclic phenols such as 3-hydroxyisoxazolyl and 3-hydoxy-1-methylpyrazolyl.

"Acidic functional group" means a group with an acidic hydrogen within it. The "corresponding protected derivatives" are those where the acidic hydrogen atom has been replaced with a suitable protecting group. For suitable protecting groups see T.W. Green and P.G.M.Wuts in "Protective Groups in Organic Chemistry" John Wiley and Sons, 1991. Exemplary acidic functional groups include carboxyl (and acid bioisosteres), hydroxy, mercapto and imidazole. Exemplary protected derivatives include esters of carboxy groups, ethers of hydroxy groups, thioethers of mercapto groups and N-benzyl derivatives of imidazoles.

"Acyl" means an H-CO- or alkyl-CO- group in which the alkyl group is as described herein.

"Acylamino" is an acyl-NH- group wherein acyl is as defined herein.

"Alkenyl" means an aliphatic hydrocarbon group containing a carbon-carbon double bond and which may be straight or branched having about 2 to about 15 carbon atoms in the chain. Preferred alkenyl groups have 2 to about 12 carbon atoms in the chain; and more preferably about 2 to about 4 carbon atoms in the chain. "Branched", as used herein and throughout the text, means that one or more lower alkyl groups such as methyl, ethyl or propyl are attached to a linear chain; here a linear alkenyl chain. "Lower alkenyl" means about 2 to about 4 carbon atoms in the chain which may be straight or branched. Exemplary alkenyl groups include ethenyl, propenyl, n-butenyl, i-butenyl, 3-methylbut-2-enyl, n-pentenyl, heptenyl, octenyl, cyclohexylbutenyl and decenyl.

"Alkenylene" means an aliphatic bivalent radical derived from a straight or branched $C_{2-6}$alkenyl group. Exemplary alkenylene radicals include vinylene and propylene.

"Alkoxy" means an alkyl-O- group in which the alkyl group is as described herein. Exemplary alkoxy groups include methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy and heptoxy.

"Alkoxycarbonyl" means an alkyl-O-CO- group in which the alkyl group is as described herein. Exemplary alkoxycarbonyl groups include methoxy- and ethoxycarbonyl.

"Alkyl" means, unless otherwise specified, an aliphatic hydrocarbon group which may be straight or branched having about 1 to about 15 carbon atoms in the chain optionally substituted by one or more halogen atoms. Particular alkyl groups have from 1 to about 6 carbon atoms. "Lower alkyl" as a group or part of a lower alkoxy group means unless otherwise specified, an aliphatic hydrocarbon group which may be straight or branched having about 1 to about 4 carbon atoms in the chain. Exemplary alkyl groups include methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl, t-butyl, n-pentyl, 3-pentyl, heptyl, octyl, nonyl, decyl and dodecyl.

"Alkylene" means an aliphatic bivalent radical derived from a straight or branched $C_{1-6}$alkyl group. Exemplary alkylene radicals include methylene, ethylene and trimethylene.

"Alkylenedioxy" means an -O-alkyl-O- group in which the alkyl group is as defined above. Exemplary alkylenedioxy groups include methylenedioxy and ethylenedioxy.

"Alkylsulphinyl" means an alkyl-SO- group in which the alkyl group is as previously described. Preferred alkylsulphinyl groups are those in which the alkyl group is $C_{1-4}$alkyl.

"Alkylsulphonyl" means an alkyl-$SO_2$- group in which the alkyl group is as previously described. Preferred alkylsulphonyl groups are those in which the alkyl group is $C_{1-4}$alkyl.

"Alkylsulphonylcarbamoyl" means an alkyl-$SO_2$-NH-C(=O)- group in which the alkyl group is as previously described. Preferred alkylsulphonylcarbamoyl groups are those in which the alkyl group is $C_{1-4}$alkyl.

"Alkylthio" means an alkyl-S- group in which the alkyl group is as previously described. Exemplary alkylthio groups include methylthio, ethylthio, isopropylthio and heptylthio.

"Alkynyl" means an aliphatic hydrocarbon group containing a carbon-carbon triple bond and which may be straight or branched having about 2 to about 15 carbon atoms in the chain. Preferred alkynyl groups have 2 to about 12 carbon atoms in the chain; and more preferably about 2 to about 4 carbon atoms in the chain. Exemplary alkynyl groups include ethynyl, propynyl, n-butynyl, i-butynyl, 3-methylbut-2-ynyl, and n-pentynyl.

"Alkynylene" means an aliphatic bivalent radical derived from a $C_{2-6}$alkynyl group. Exemplary alkenylene radicals include ethynylene and propynylene.

"Aroyl" means an aryl-CO- group in which the aryl group is as described herein. Exemplary aroyl groups include benzoyl and 1- and 2-naphthoyl.

"Aroylamino" is an aroyl-NH- group wherein aroyl is as previously defined.

"Aryl" as a group or part of a group denotes: (i) an optionally substituted monocyclic or multicyclic aromatic carbocyclic moiety of about 6 to about 14 carbon atoms, such as phenyl or naphthyl; or (ii) an optionally substituted partially saturated multicyclic aromatic carbocyclic moiety in which an aryl and a cycloalkyl or cycloalkenyl group are fused together to form a cyclic structure, such as a tetrahydronaphthyl, indenyl or indanyl ring. Aryl groups may be

substituted with one or more aryl group substituents which may be the same or different, where "aryl group substituent" includes, for example, acyl, acylamino, alkoxy, alkoxycarbonyl, alkylenedioxy, alkylsulphinyl, alkylsulphonyl, alkylthio, aroyl, aroylamino, aryl, arylalkyloxy, arylalkyloxycarbonyl, arylalkylthio, aryloxy, aryloxycarbonyl, arylsulphinyl, arylsulphonyl, arylthio, carboxy, cyano, halo, heteroaroyl, heteroaryl, heteroarylalkyloxy, heteroaroylamino, heteroaryloxy, hydroxy, nitro, trifluoromethyl, $Y^6Y^7N$-, $Y^6Y^7NCO$-, $Y^6Y^7NSO_2$-(where $Y^6$ and $Y^7$ are independently hydrogen, alkyl, aryl, heteroaryl, arylalkyl and heteroarylalkyl), $Y^6Y^7N$-$C_{2-6}$alkylene-$Z^2$- (where $Z^2$ is O, $NR^9$ or S(O)q), alkylC(=O)-$Y^6N$-, alkyl$SO_2$-$Y^6N$- or alkyl optionally substituted with aryl, heteroaryl, hydroxy, or $Y^6Y^7N$-.

"Arylalkenyl" means an aryl-alkenyl- group in which the aryl and alkenyl moieties are as previously described.

"Arylalkyl" means an aryl-alkyl- group in which the aryl and alkyl moieties are as previously described. Preferred arylalkyl groups contain a $C_{1-4}$alkyl moiety. Exemplary arylalkyl groups include benzyl, 2-phenethyl and naphthlenemethyl.

"Arylalkyloxy" means an arylalkyl-O- group in which the arylalkyl groups is as previously described. Exemplary arylalkyloxy groups include benzyloxy and 1- or 2-naphthalenemethoxy.

"Arylalkyloxycarbonyl" means an arylalkyl-O-CO- group in which the arylalkyl groups is as previously described. An exemplary arylalkyloxycarbonyl group is benzyloxycarbonyl.

"Arylalkylthio" means an arylalkyl-S- group in which the arylalkyl group is as previously described. An exemplary arylalkylthio group is benzylthio.

"Arylalkynyl" means an aryl-alkynyl- group in which the aryl and alkynyl moieties are as previously described.

"Aryloxy" means an aryl-O- group in which the aryl group is as previously described. Exemplary aryloxy groups include optionally substituted phenoxy and naphthoxy.

"Aryloxycarbonyl" means an aryl-O-CO- group in which the aryl group is as previously described. Exemplary aryloxycarbonyl groups include phenoxycarbonyl and naphthoxycarbonyl.

"Arylsulphinyl" means an aryl-SO- group in which the aryl group is as previously described.

"Arylsulphonyl" means an aryl-$SO_2$- group in which the aryl group is as previously described.

"Arylsulphonylcarbamoyl" means an aryl-$SO_2$-NH-C(=O)- group in which the aryl group is as previously described.

"Arylthio" means an aryl-S- group in which the aryl group is as previously described. Exemplary arylthio groups include phenylthio and naphthylthio.

"Azaheteroaryl" means an aromatic carbocyclic moiety of about 5 to about 10 ring members in which one of the ring members is nitrogen and the other ring members are chosen from carbon, oxygen, sulphur, or nitrogen. Examples of azaheteroaryl groups include pyridyl, pyrimidinyl, quinolinyl, isoquinolinyl, quinazolinyl, imidazolyl, and benzimidazolyl.

"Cycloalkenylene" means a bivalent radical derived from an unsaturated monocyclic hydrocarbon of about 3 to about 10 carbon atoms by removing a hydrogen atom from each of two different carbon atoms of the ring. Exemplary cycloalkenylene radicals include cyclopentenylene and cyclohexenylene.

"Cycloalkenyl" means a non-aromatic monocyclic or multicyclic ring system containing at least one carbon-carbon double bond and having about 3 to about 10 carbon atoms. Exemplary monocyclic cycloalkenyl rings include cyclopentenyl, cyclohexenyl or cycloheptenyl.

"Cycloalkenylalkyl" means a cycloalkenyl-alkyl- group in which the cycloalkenyl and alkyl moieties are as previously described.

"Cycloalkylalkenyl" means a cycloalkyl-alkenyl- group in which the cycloalkyl and alkenyl moieties are as previously described.

"Cycloalkyl" means a saturated monocyclic or bicyclic ring system of about 3 to about 10 carbon atoms optionally substituted by oxo. Exemplary monocyclic cycloalkyl rings include $C_{3-8}$cycloalkyl rings such as cyclopropyl, cyclopentyl, cyclohexyl and cycloheptyl.

"Cycloalkylalkyl" means a cycloalkyl-alkyl- group in which the cycloalkyl and alkyl moieties are as previously described. Exemplary monocyclic cycloalkylalkyl groups include cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl and cycloheptylmethyl.

"Cycloalkylalkenyl" means a cycloalkyl-alkenyl- group in which the cycloalkyl and alkenyl moieties are as previously described.

"Cycloalkylalkynyl" means a cycloalkyl-alkynyl- group in which the cycloalkyl and alkynyl moieties are as previously described.

"Cycloalkylene" means a bivalent radical derived from a saturated monocyclic hydrocarbon of about 3 to about 10 carbon atoms by removing a hydrogen atom from each of two different carbon atoms of the ring. Exemplary cycloalkylene radicals include cyclopentylene and cyclohexylene.

"Halo" or "halogen" means fluoro, chloro, bromo, or iodo. Preferred are fluoro or chloro.

"Heteroaroyl" means a heteroaryl-CO- group in which the heteroaryl group is as described herein. Exemplary groups include pyridylcarbonyl.

"Heteroaroylamino" means a heteroaroyl-NH- group in which the heteroaryl moiety are as previously described.

"Heteroaryl" as a group or part of a group denotes: (i) an optionally substituted aromatic monocyclic or multicyclic organic moiety of about 5 to about 10 ring members in which one or more of the ring members is/are element(s) other than carbon, for example nitrogen, oxygen or sulphur (examples of such groups include benzimidazolyl, benzthiazolyl, furyl, imidazolyl, indolyl, indolizinyl, isoxazolyl, isoquinolinyl, isothiazolyl, oxadiazolyl, pyrazinyl, pyridazinyl, pyrazolyl, pyridyl, pyrimidinyl, pyrrolyl, quinazolinyl, quinolinyl, 1,3,4-thiadiazolyl, thiazolyl, thienyl and triazolyl groups, optionally substituted by one or more aryl group substituents as defined above); (ii) an optionally substituted partially saturated multicyclic heterocarbocyclic

moiety in which a heteroaryl and a cycloalkyl or cycloalkenyl group are fused together to form a cyclic structure (examples of such groups include pyrindanyl groups). Optional substituents include one or more "aryl group substituents" as defined above. When $R^1$ or $R^4$ contains an optionally substituted heteroaryl group this may particularly represent an optionally substituted "azaheteroaryl" group.

"Heteroarylalkenyl" means a heteroaryl-alkenyl- group in which the heteroaryl and alkenyl moieties are as previously described.

"Heteroarylalkynyl" means a heteroaryl-alkynyl- group in which the heteroaryl and alkynyl moieties are as previously described.

"Heteroarylalkyl" means a heteroaryl-alkyl- group in which the heteroaryl and alkyl moieties are as previously described. Preferred heteroarylalkyl groups contain a $C_{1-4}$alkyl moiety. Exemplary heteroarylalkyl groups include pyridylmethyl.

"Heteroarylalkyloxy" means an heteroarylalkyl-O- group in which the heteroarylalkyl group is as previously described. Exemplary heteroaryloxy groups include optionally substituted pyridylmethoxy.

"Heteroaryldiyl" means a bivalent radical derived from an optionally substituted aromatic monocyclic or multicyclic organic moiety of about 5 to about 10 ring members in which one or more of the ring members is/are element(s) other than carbon, for example nitrogen, oxygen or sulphur., and optionally substituted by one or more aryl group substituents as defined above. When $Ar^1$ is a heteroaryldiyl radical this may particularly represent an optionally substituted pyridindiyl or an optionally substituted benzoxazoldiyl.

"Heteroaryloxy" means an heteroaryl-O- group in which the heteroaryl group is as previously described. Exemplary heteroaryloxy groups include optionally substituted pyridyloxy.

"Heteroarylsulphonylcarbamoyl" means a heteroaryl-$SO_2$-NH-C(=O)- group in which the heteroaryl group is as previously described.

"Heterocycloalkyl" means: (i) a cycloalkyl group of about 3 to 7 ring members which contains one or more heteroatoms selected from O, S or $NY^8$ (where $Y^8$ is hydrogen, alkyl, arylalkyl, and

aryl); (ii) an optionally substituted partially saturated multicyclic heterocarbocyclic moiety in which an aryl (or heteroaryl ring) and a heterocycloalkyl group are fused together to form a cyclic structure (examples of such groups include chromanyl, dihydrobenzofuranyl, indolinyl and pyrindolinyl groups.

"Heterocycloalkylalkyl" means a heterocycloalkyl-alkyl- group in which the heterocycloalkyl and alkyl moieties are as previously described.

"Heterocycloalkylene" means a bivalent radical derived from a saturated monocyclic hydrocarbon of about 5 to about 7 atoms, which contains one or more heteroatoms selected from O, S or $NY^8$ (where $Y^8$ is hydrogen, alkyl, arylalkyl, and aryl) and is optionally substituted by oxo, by removing a hydrogen atom from each of two different carbon atoms of the ring, or when $NY^8$ is NH by removing a hydrogen atom from one carbon atom of the ring and a hydrogen atom from the NH, or when the ring contains two $NY^8$ heteroatoms and $NY^8$ is NH by removing a hydrogen atom from both nitrogen atoms.

"Hydroxyalkyl" means a HO-alkyl- group in which alkyl is as previously defined. Preferred hydroxyalkyl groups contain $C_{1-4}$alkyl for example hydroxymethyl and 2-hydroxyethyl.

"$Y^6Y^7N$-" means a substituted or unsubstituted amino group, wherein $Y^6$ and $Y^7$ are as previously described. Exemplary groups include amino ($H_2N$-), methylamino, ethylmethylamino, dimethylamino and diethylamino.

"$Y^6Y^7NCO$-" means a substituted or unsubstituted carbamoyl group, wherein $Y^6$ and $Y^7$ are as previously described. Exemplary groups are carbamoyl ($H_2NCO$-) and dimethylcarbamoyl ($Me_2NCO$-).

"$Y^6Y^7NSO_2$-" means a substituted or unsubstituted sulphamoyl group, wherein $Y^6$ and $Y^7$ are as previously described. Exemplary groups are sulphamoyl ($H_2NSO_2$-) and dimethylsulphamoyl ($Me_2NSO_2$-).

"Phenylene" means an optionally substituted bivalent radical derived from a phenyl group. Suitable substituents include one or more "aryl group substituents" as defined above, particularly halogen, methyl or methoxy.

"Prodrug" means a compound which is convertible in vivo by metabolic means (e.g. by hydrolysis) to a compound of formula (I), including N-oxides thereof. For example an ester of a compound of formula (I) containing a hydroxy group may be convertible by hydrolysis in vivo to the parent molecule. Alternatively an ester of a compound of formula (I) containing a carboxy group may be convertible by hydrolysis in vivo to the parent molecule.

Suitable esters of compounds of formula (I) containing a hydroxy group, are for example acetates, citrates, lactates, tartrates, malonates, oxalates, salicylates, propionates, succinates, fumarates, maleates, methylene-bis-β-hydroxynaphthoates, gentisates, isethionates, di-p-toluoyltartrates, methanesulphonates, ethanesulphonates, benzenesulphonates, p-toluenesulphonates, cyclohexylsulphamates and quinates.

An especially useful class of esters of compounds of formula (I) containing a hydroxy group, may be formed from acid moieties selected from those described by Bundgaard et. al., J. Med. Chem., 1989, 32 , page 2503-2507, and include substituted (aminomethyl)-benzoates, for example dialkylamino-methylbenzoates in which the two alkyl groups may be joined together and/or interrupted by an oxygen atom or by an optionally substituted nitrogen atom, e.g. an alkylated nitrogen atom, more especially (morpholino-methyl)benzoates, e.g. 3- or 4-(morpholinomethyl)-benzoates, and (4-alkylpiperazin-1-yl)benzoates, e.g. 3- or 4-(4-alkylpiperazin-1-yl)benzoates.

Where the compound of the invention contains a carboxy group, or a sufficiently acidic bioisostere, base addition salts may be formed and are simply a more convenient form for use; and in practice, use of the salt form inherently amounts to use of the free acid form. The bases which can be used to prepare the base addition salts include preferably those which produce, when combined with the free acid, pharmaceutically acceptable salts, that is, salts whose cations are non-toxic to the patient in pharmaceutical doses of the salts, so that the beneficial inhibitory effects inherent in the free base are not vitiated by side effects ascribable to the cations. Pharmaceutically acceptable salts, including those derived from alkali and alkaline earth metal salts, within the scope of the invention include those derived from the following bases: sodium hydride, sodium hydroxide, potassium hydroxide, calcium hydroxide, aluminium hydroxide, lithium hydroxide, magnesium hydroxide, zinc hydroxide, ammonia, ethylenediamine, N-methyl-glucamine, lysine, arginine, ornithine, choline, N,N'-dibenzylethylenediamine, chloroprocaine, diethanolamine, procaine, N-benzylphenethylamine, diethylamine, piperazine, tris(hydroxymethyl)aminomethane, tetramethylammonium hydroxide, and the like.

Some of the compounds of the present invention are basic, and such compounds are useful in the form of the free base or in the form of a pharmaceutically acceptable acid addition salt thereof.

Acid addition salts are a more convenient form for use; and in practice, use of the salt form inherently amounts to use of the free base form. The acids which can be used to prepare the acid addition salts include preferably those which produce, when combined with the free base, pharmaceutically acceptable salts, that is, salts whose anions are non-toxic to the patient in pharmaceutical doses of the salts, so that the beneficial inhibitory effects inherent in the free base are not vitiated by side effects ascribable to the anions. Although pharmaceutically acceptable salts of said basic compounds are preferred, all acid addition salts are useful as sources of the free base form even if the particular salt, per se, is desired only as an intermediate product as, for example, when the salt is formed only for purposes of purification, and identification, or when it is used as intermediate in preparing a pharmaceutically acceptable salt by ion exchange procedures. Pharmaceutically acceptable salts within the scope of the invention include those derived from mineral acids and organic acids, and include hydrohalides, e.g. hydrochlorides and hydrobromides, sulphates, phosphates, nitrates, sulphamates, acetates, citrates, lactates, tartrates, malonates, oxalates, salicylates, propionates, succinates, fumarates, maleates, methylene-bis-b-hydroxynaphthoates, gentisates, isethionates, di-p-toluoyltartrates, methane-sulphonates, ethanesulphonates, benzenesulphonates, p-toluenesulphonates, cyclohexylsulphamates and quinates.

As well as being useful in themselves as active compounds, salts of compounds of the invention are useful for the purposes of purification of the compounds, for example by exploitation of the solubility differences between the salts and the parent compounds, side products and/or starting materials by techniques well known to those skilled in the art.

With reference to formula (I) above, the following are particular and preferred groupings:

$R^1$ may particularly represent a group $R^5$-$L^4$-$R^7$-$L^5$- in which $L^5$ represents a -C(=O)- linkage, $R^7$ is a straight or branched $C_{1-6}$alkylene chain (especially ethylene), $L^4$ is -O-C(=O)-NH- and $R^5$ is arylalkyl (the aryl ring of which is optionally substituted) or heteroarylalkyl (the heteroaryl ring of which is optionally substituted).

$R^1$ may also particularly represent a group $R^5$-$L^4$-$Ar^1$-$L^3$- in which $L^3$ represents a -C(=O)- linkage, $Ar^1$ is optionally substituted phenylene, such as optionally substituted *m*- or *p*-phenylene, preferably optionally substituted *p*-phenylene, more preferably a 3-substituted *p*-phenylene (preferred optional substituents include $C_{1-4}$alkyl and $C_{1-4}$alkoxy, especially methyl and methoxy), or $Ar^1$ is an optionally substituted heteroaryldiyl, such as optionally substituted pyridinediyl, preferably an optionally substituted *p*-pyridinediyl (preferred optional substituents include $C_{1-4}$alkyl and $C_{1-4}$alkoxy, especially methyl and methoxy), more preferably a pyridine-2,5-diyl which is substituted in the 4- or 6-position with a methyl or methoxy group, $L^4$ represents a -NH-C(=O)-NH- linkage, and $R^5$ is an optionally substituted aryl group such as 2-substituted or 3-substituted phenyl, and is preferably 2- or 3-methyl(or methoxy)phenyl, or $R^5$ is an optionally substituted heteroaryl group, such as optionally substituted pyridyl, and is preferably 3-methyl-2-pyridyl.

$R^1$ may also particularly represent a group $R^5$-$L^4$-$Ar^1$-$R^7$-$L^5$- in which $L^5$ represents a -C(=O)- linkage, $R^7$ is a straight or branched $C_{1-6}$alkylene chain (especially methylene or ethylene, preferably methylene), $Ar^1$ is an optionally substituted phenylene, such as optionally substituted *m*- or *p*-phenylene, preferably optionally substituted *p*-phenylene, more preferably a 3-substituted *p*-phenylene (preferred optional substituents include $C_{1-4}$alkyl and $C_{1-4}$alkoxy, especially methyl and methoxy), or $Ar^1$ is an optionally substituted heteroaryldiyl, such as optionally substituted pyridinediyl, preferably an optionally substituted *p*-pyridinediyl (preferred optional substituents include $C_{1-4}$alkyl and $C_{1-4}$alkoxy, especially methyl and methoxy), more preferably a pyridine-2,5-diyl which is substituted in the 4- or 6-position with a methyl or methoxy group, $L^4$ represents a -NH-C(=O)-NH- linkage, and $R^5$ is an optionally substituted aryl group such as 2-substituted or 3-substituted phenyl, and is preferably 2- or 3-methyl(or methoxy)phenyl, or $R^5$ is an optionally substituted heteroaryl group, such as optionally substituted pyridyl, and is preferably 3-methyl-2-pyridyl.

$R^2$ may particularly represent hydrogen.

$R^2$ may also particularly represent $C_{1-4}$alkyl (e.g. methyl).

$R^3$ may particularly represent hydrogen.

$R^3$ may also particularly represent $C_{1-4}$alkyl (e.g. methyl).

$R^4$ may particularly represent hydrogen.

$R^4$ may also particularly represent $C_{1-4}$alkyl (e.g. methyl).

$R^4$ may also particularly represent $C_{1-4}$alkyl substituted by aryl, especially arylmethyl or arylethyl. Exemplary aryl groups include phenyl optionally substituted by one or more "aryl group substituents", for example alkylphenyl, alkoxyphenyl, dialkoxyphenyl, piperonyl, halophenyl, dialkylaminophenyl, trifluoromethyl and methanesulphonylphenyl, especially dialkoxyphenyl such as 3,4-dimethoxyphenyl.

$R^4$ may also particularly represent $C_{1-4}$alkyl substituted by heteroaryl, especially azaheteroaryl. Exemplary heteroaryl groups include optionally substituted indolyl, imidazolyl, pyridyl and furyl. $R^4$ especially represents 3-(imidazol-1-yl)-propyl.

$R^4$ may also particularly represent $C_{1-4}$alkyl substituted by $-NY^1Y^2$. Exemplary $-NY^1Y^2$ groups include acylamino, aryl(alkylamino) and 5-7 membered cyclic amines such as morpholine, piperidine, pyrrolidine and 2-oxo-pyrrolidine. $R^4$ especially represents 3-(2-oxo-pyrrolidin-1-yl)-propyl or 3-(N-methyl-N-phenyl-amino)propyl.

$R^4$ may also particularly represent $C_{1-4}$alkyl substituted by cycloalkyl. Exemplary cycloalkyl groups include cyclohexyl and cyclopentyl.

$R^4$ may also particularly represent $C_{1-4}$alkyl substituted by alkoxy.

$R^4$ may also particularly represent $C_{1-4}$alkyl substituted by halo.

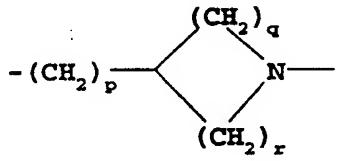
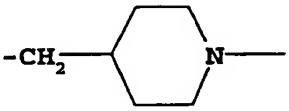
$R^4$ may also particularly represent lower alkenyl (e.g. allyl).

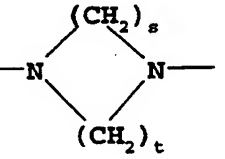
$R^3$ and $R^4$ together may particularly represent -C(=O)-CH=CH-.

$L^1$ may particularly represent a straight chain $C_{2-6}$alkylene, especially ethylene and trimethylene.

$L^1$ may also particularly represent -$Ar^2$-, especially where $Ar^2$ is cycloalkylene (particularly (cyclohexylene).

$L^1$ may also particularly represent a -$CH_2$-$Ar^2$-$CH_2$- linkage, especially where $Ar^2$ is arylene (particularly phenylene).

The group -$L^1$-N($R^3$)- may also particularly represent  , preferably where p is 0 or 1 and q+r is 3 or 4, especially  .

The group -N($R^2$)-$L^1$-N($R^3$)- may also particularly represent  , preferably 1,4-piperazindiyl or 1,4-homopiperazindiyl.

$L^2$ may particularly represent a straight or branched $C_{1-4}$alkylene linkage. Exemplary $C_{1-4}$alkylene linkages include methylene, ethylene, trimethylene, -$CH_2$-$CH(CH_3)$-, -$CH(CH_3)$-$CH_2$- and tetramethylene.

$L^2$ may also particularly represent a straight or branched $C_{1-4}$alkylene linkage substituted by a group chosen from alkenyl, alkynyl, aryl, carboxy (or an acid bioisostere), cyano, cycloalkenyl, cycloalkyl, heteroaryl, heterocycloalkyl, oxo, -C(=O)$R^9$, -C(=O)O$R^9$, -C(=O)N$Y^1Y^2$ or -N$Y^1Y^2$, or by alkyl substituted by aryl, carboxy (or an acid bioisostere), cyano, heteroaryl,

heterocycloalkyl, hydroxy, mercapto, $-C(=O)R^9$, $-C(=O)OR^9$, $-C(=O)NY^1Y^2$, $-OR^9$, $S(O)_vR^9$, $-NHC(=O)OAlkyl$, $-NY^1Y^2$, $-NR^{10}C(=Z)-NY^4Y^5$ or $-NH-C(=NH)NH_2$.

Y may particularly represent carboxy.

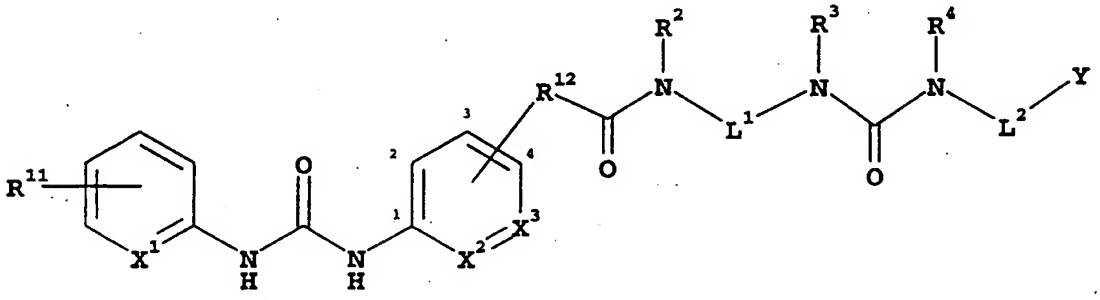
Y may also particularly represent an acid bioisostere.

m may particularly represent zero.

m may also particularly represent 1.

It is to be understood that this invention covers all appropriate combinations of the particular and preferred groupings referred to herein.

A particular group of compounds of the invention are compounds of formula (Ia):-



(Ia)

in which $R^2$, $R^3$, $R^4$, $L^1$, $L^2$ and Y are as hereinbefore defined, $R^{11}$ is hydrogen, halogen, lower alkyl or lower alkoxy, $R^{12}$ is a direct bond or an alkylene chain, $X^1$, $X^2$ and $X^3$ independently represent N or $CR^{13}$ (where $R^{13}$ is hydrogen, halogen, lower alkyl or lower alkoxy), and $-R^{12}-C(=O)-N(R^2)-L^1-N(R^3)-C(=O)-N(R^4)-L^2-Y$ is attached at the ring 3 or 4 position, and their prodrugs and pharmaceutically acceptable salts, and solvates (e.g. hydrates) of compounds of formula (Ia) and their prodrugs.

Compounds of formula (Ia) in which $R^2$ represents hydrogen are preferred.

Compounds of formula (Ia) in which $R^2$ represents $C_{1-4}$alkyl (e.g. methyl) are also preferred.

Compounds of formula (Ia) in which $R^3$ represents hydrogen are preferred.

Compounds of formula (Ia) in which $R^3$ represents $C_{1-4}$alkyl (e.g. methyl) are also preferred.

Compounds of formula (Ia) in which $R^4$ represents hydrogen are preferred.

Compounds of formula (Ia) in which $R^4$ represents $C_{1-4}$alkyl (e.g. methyl) are also preferred.

Compounds of formula (Ia) in which $R^4$ represents $C_{1-4}$alkyl substituted by aryl are also preferred. Exemplary aryl groups include phenyl optionally substituted by one or more "aryl group substituents", for example alkylphenyl, alkoxyphenyl, dialkoxyphenyl, piperonyl, halophenyl, dialkylaminophenyl, trifluoromethyl and methanesulphonylphenyl, especially dialkoxyphenyl such as 3,4-dimethoxyphenyl.

Compounds of formula (Ia) in which $R^4$ represents alkyl substituted by heteroaryl, especially azaheteroaryl, are also preferred. Exemplary heteroaryl groups include optionally substituted indolyl, imidazolyl, pyridyl and furyl. Compounds of formula (Ia) in which $R^4$ represents 3-(imidazol-1-yl)-propyl are especially preferred.

Compounds of formula (Ia) in which $R^4$ represents $C_{1-4}$alkyl substituted by $-NY^1Y^2$ are also preferred. Exemplary $-NY^1Y^2$ groups include acylamino, aryl(alkylamino) and 5-7 membered cyclic amines such as morpholine, piperidine, pyrrolidine and 2-oxo-pyrrolidine. Compounds of formula (Ia) in which $R^4$ represents 3-(2-oxo-pyrrolidin-1-yl)-propyl are especially preferred.

Compounds of formula (Ia) in which $R^4$ represents $C_{1-4}$alkyl substituted by cycloalkyl are also preferred. Exemplary cycloalkyl groups include cyclohexyl and cyclopentyl.

Compounds of formula (Ia) in which $R^4$ represents $C_{1-4}$alkyl substituted by alkoxy are also preferred.

Compounds of formula (Ia) in which $R^4$ represents $C_{1-4}$alkyl substituted by halo are also preferred.

Compounds of formula (Ia) in which $R^4$ represents lower alkenyl (e.g. allyl) are also preferred.

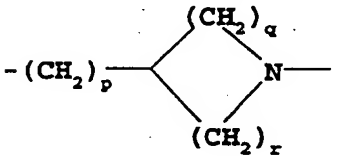
Compounds of formula (Ia) in which $R^3$ and $R^4$ together represent -C(=O)-CH=CH- are also preferred.

Compounds of formula (Ia) in which $L^1$ represents a straight chain $C_{2-6}$alkylene, especially ethylene and trimethylene, are preferred.

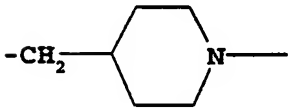
Compounds of formula (Ia) in which $L^1$ represents a -$Ar^2$- linkage, especially where $Ar^2$ is cycloalkylene (particularly cyclohexylene), are also preferred.

Compounds of formula (Ia) in which $L^1$ represents a -$CH_2$-$Ar^2$-$CH_2$- linkage, especially where $Ar^2$ is arylene (particularly phenylene), are also preferred.

Compounds of formula (Ia) in which the group -$L^1$-N($R^3$)- represents

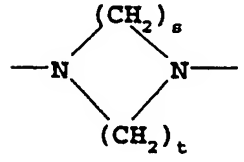


, preferably where p is 0 or 1 and q+r is 3 or 4, especially



are also preferred.

Compounds of formula (Ia) in which the group -N($R^2$)-$L^1$-N($R^3$)- represents



, preferably 1,4-piperazindiyl or 1,4-homopiperazindiyl, are also preferred.

Compounds of formula (Ia) in which $L^2$ represents a straight or branched $C_{1-4}$alkylene linkage are preferred. Exemplary $C_{1-4}$alkylene linkages include methylene, ethylene, trimethylene, $-CH_2-CH(CH_3)-$, $-CH(CH_3)-CH_2-$ and tetramethylene.

Compounds of formula (Ia) in which $L^2$ represents a straight or branched $C_{1-4}$alkylene linkage substituted by a group chosen from alkenyl, alkynyl, aryl, carboxy (or an acid bioisostere), cyano, cycloalkenyl, cycloalkyl, heteroaryl, heterocycloalkyl, $-C(=O)R^9$, $-C(=O)OR^9$, $-C(=O)NY^1Y^2$ or $-NY^1Y^2$, or by alkyl substituted by aryl, carboxy (or an acid bioisostere), cyano, heteroaryl, heterocycloalkyl, hydroxy, mercapto, $-C(=O)R^9$, $-C(=O)OR^9$, $-C(=O)NY^1Y^2$, $-OR^9$, $S(O)_vR^9$, -NHC(=O)OAlkyl, $-NY^1Y^2$, $-NR^{10}C(=Z)-NY^4Y^5$ or $-NH-C(=NH)NH_2$ are also preferred.

Compounds of formula (Ia) in which $R^{11}$ represents hydrogen are preferred.

Compounds of formula (Ia) in which $R^{12}$ represents a direct bond are preferred.

Compounds of formula (Ia) in which $R^{12}$ represents a straight $C_{1-4}$alkylene chain, more especially ethylene or particularly methylene, are also preferred.

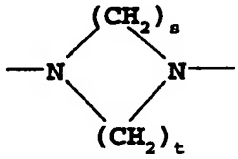
Compounds of formula (Ia) in which $X^1$ represents $CR^{13}$, especially where $R^{13}$ is lower alkyl or lower alkoxy (e.g. methyl or methoxy), especially methyl, are preferred.

Compounds of formula (Ia) in which $X^2$ represents $CR^{13}$, especially where $R^{13}$ is hydrogen or lower alkoxy (e.g. methoxy), especially methoxy, are also preferred.

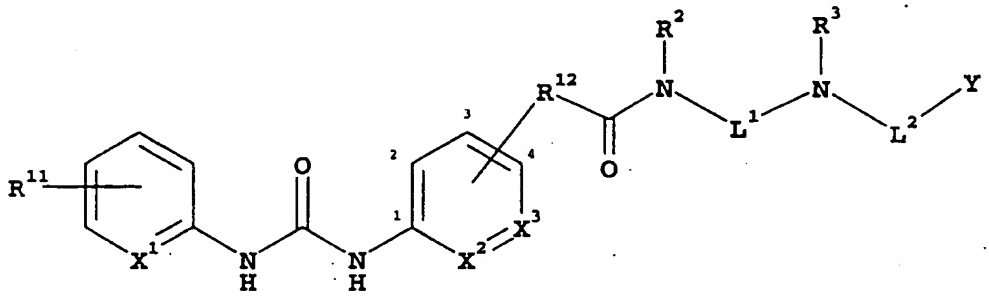
Compounds of formula (Ia) in which $X^3$ represents CH are also preferred.

Compounds of formula (Ia) in which Y represents carboxy are preferred.

The group - $R^{12}-C(=O)-N(R^2)-L^1-N(R^3)-C(=O)-N(R^4)-L^2-Y$ may preferably be attached at the ring 4 position.

A preferred group of compounds of the invention are compounds of formula (Ia) in which:- $R^2$ is hydrogen or $C_{1-4}$alkyl (e.g. methyl) and $R^3$ is hydrogen or $C_{1-4}$alkyl (e.g. methyl); $R^4$ is hydrogen, $C_{1-4}$alkyl substituted by aryl (especially 4-dimethylaminophenyl-$C_{1-2}$alkyl and 3,4-dimethoxyphenyl-$C_{1-2}$alkyl), $C_{1-4}$alkyl substituted by $-NY^1Y^2$ [for example aryl(alkylamino)-$C_{1-4}$alkyl and heterocyclyl-$C_{1-4}$alkyl, preferably (2-oxo-pyrrolidin-1-yl)propyl], or $R^3$ and $R^4$ together represent -C(=O)-CH=CH-; $L^1$ is a straight $C_{2-6}$alkylene chain (especially ethylene), cycloalkylene (especially cyclohexylene); or the group $-N(R^2)-L^1-N(R^3)-$ represents  (especially 1,4-piperazindiyl or 1,4-homopiperazindiyl); $L^2$ is a straight or branched $C_{1-4}$alkylene chain (especially $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, $-CH(CH_3)CH_2-$), or a $C_{1-4}$alkylene chain substituted by $-C(=O)-NY^1Y^2$ [especially $-CH(CONH_2)-CH_2-$]; $R^{11}$ is hydrogen; $R^{12}$ is a bond or a straight $C_{1-4}$alkylene chain (especially methylene); $X^1$ represents $CR^{13}$ (especially C-methyl); $X^2$ represents $CR^{13}$ (especially C-methoxy); $X^3$ represents CH; Y represents carboxy; and the group $-R^{12}-C(=O)-N(R^2)-L^1-N(R^3)-C(=O)-N(R^4)-L^2-Y$ is attached at the ring 4 position; and their prodrugs, and pharmaceutically acceptable salts and solvates (e.g. hydrates) of such compounds and their prodrugs.

Another particular group of compounds of the invention are compounds of formula (Ib):-



(Ib)

in which $R^2$, $R^3$, $L^1$, $L^2$ and Y are as hereinbefore defined, $R^{11}$ is hydrogen, halogen, lower alkyl or lower alkoxy, $R^{12}$ is a direct bond or an alkylene chain, $X^1$, $X^2$ and $X^3$ independently represent N or $CR^{13}$ (where $R^{13}$ is hydrogen, halogen, lower alkyl or lower alkoxy), and $-R^{12}-C(=O)-N(R^2)-L^1-N(R^3)-L^2-Y$ is attached at the ring 3 or 4 position, and their prodrugs and pharmaceutically acceptable salts, and solvates (e.g. hydrates) of compounds of formula (Ib) and their prodrugs.

Compounds of formula (Ib) in which $R^2$ represents hydrogen are preferred.

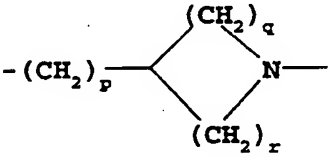
Compounds of formula (Ib) in which $R^2$ represents $C_{1-4}$alkyl (e.g. methyl) are also preferred.

Compounds of formula (Ib) in which $R^3$ represents hydrogen are preferred.

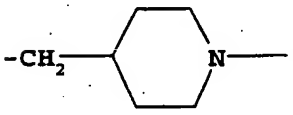
Compounds of formula (Ib) in which $R^3$ represents $C_{1-4}$alkyl (e.g. methyl) are also preferred.

Compounds of formula (Ib) in which $L^1$ represents a straight chain $C_{2-6}$alkylene, especially ethylene or trimethylene, are preferred.

Compounds of formula (Ib) in which the group $-L^1-N(R^3)-$ represents

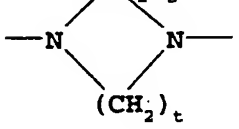


, particularly where p is 0 or 1 and q+r is 3 or 4, especially



, are also preferred.

Compounds of formula (Ib) in which the group $-N(R^2)-L^1-N(R^3)-$ represents



, especially 1,4-piperazindiyl or 1,4-homopiperazindiyl, are also preferred.

Compounds of formula (Ib) in which $L^2$ represents a straight or branched $C_{1-4}$alkylene linkage are preferred. Exemplary $C_{1-4}$alkylene linkages include methylene, ethylene, trimethylene, $-CH_2-CH(CH_3)-$, $-CH(CH_3)-CH_2-$ and tetramethylene.

Compounds of formula (Ib) in which $L^2$ represents a straight or branched $C_{1-4}$alkylene linkage substituted by a group chosen from alkenyl, alkynyl, aryl, carboxy (or an acid bioisostere), cyano, cycloalkenyl, cycloalkyl, heteroaryl, heterocycloalkyl, oxo, $-C(=O)R^9$, $-C(=O)OR^9$, $-C(=O)NY^1Y^2$ or $-NY^1Y^2$, or by alkyl substituted by aryl, carboxy (or an acid bioisostere), cyano, heteroaryl, heterocycloalkyl, hydroxy, mercapto, $-C(=O)R^9$, $-C(=O)OR^9$, $-C(=O)NY^1Y^2$, $-OR^9$, $S(O)_vR^9$, -NHC(=O)OAlkyl, $-NY^1Y^2$, $-NR^{10}C(=Z)-NY^4Y^5$ or $-NH-C(=NH)NH_2$ are also preferred.

Compounds of formula (Ib) in which $R^{11}$ represents hydrogen are preferred.

Compounds of formula (Ib) in which $R^{12}$ represents a direct bond are preferred.

Compounds of formula (Ib) in which $R^{12}$ represents a straight $C_{1-4}$alkylene chain, more especially ethylene or particularly methylene, are also preferred.

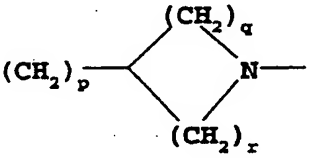
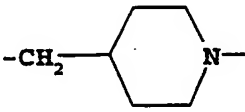
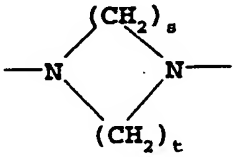
Compounds of formula (Ib) in which $X^1$ represents $CR^{13}$, especially where $R^{13}$ is lower alkyl or lower alkoxy (e.g. methyl or methoxy), especially methyl, are preferred.

Compounds of formula (Ib) in which $X^2$ represents $CR^{13}$, especially where $R^{13}$ is hydrogen or lower alkoxy (e.g. methoxy), especially methoxy, are also preferred.

Compounds of formula (Ib) in which $X^3$ represents CH are also preferred.

Compounds of formula (Ib) in which Y represents carboxy are preferred.

The group $-R^{12}-C(=O)-N(R^2)-L^1-N(R^3)-L^2-Y$ may preferably be attached at the ring 4 position.

A preferred group of compounds of the invention are compounds of formula (Ib) in which:- $R^2$ is hydrogen; $R^3$ is hydrogen or $C_{1-4}$alkyl (e.g. methyl); $L^1$ is a straight $C_{2-6}$alkylene chain (especially trimethylene),or the group $-L^1-N(R^3)-$ represents 
where p is 0 or 1 and q+r is 3 or 4 (especially  ), or the group $-N(R^2)-L^1-N(R^3)-$ represents  especially 1,4-piperazindiyl or 1,4-homopiperazindiyl; $L^2$ is a straight or branched $C_{1-4}$alkylene chain (especially $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, $-CH(CH_3)CH_2-$), or a $C_{1-4}$alkylene chain substituted by oxo [especially $-C(=O)-CH_2-CH_2-$] or a $C_{1-4}$alkylene chain substituted by $-C(=O)-NY^1Y^2$ [especially $-CH(CONH_2)-CH_2-$]; $R^{11}$ is hydrogen; $R^{12}$ is a straight $C_{1-4}$alkylene chain (especially ethylene or particularly methylene); $X^1$ represents $CR^{13}$ (especially C-methyl); $X^2$ represents $CR^{13}$ (especially C-methoxy); $X^3$ represents CH; Y represents carboxy; and the group $-R^{12}-C(=O)-N(R^2)-L^1-N(R^3)-L^2-Y$ is attached at the ring 4 position; and their prodrugs, and pharmaceutically acceptable salts and solvates (e.g. hydrates) of such compounds and their prodrugs.

Particular compounds of the invention are selected from the following:

Compounds A to DB;

3-{3-(2-{2-[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylamino}-ethyl)-1-[3-(2-oxo-pyrrolidin-1-yl)-propyl]-ureido}-propionic acid, Compound DC;

3-{3-(3-{2-[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylamino}-propyl)-1-[3-(2-oxo-pyrrolidin-1-yl)-propyl]-ureido}-propionic acid, Compound DD;

3-{3-(3-{2-[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylamino}-2,2-dimethyl-propyl)-1-[3-(2-oxo-pyrrolidin-1-yl)-propyl]-ureido}-propionic acid, Compound DE;

3-{3-[3-({[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetyl}-methyl-amino)-propyl]-3-methyl-1-[3-(2-oxo-pyrrolidin-1-yl)-propyl]-ureido}-propionic acid, Compound DF;

3-{3-[2-({[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetyl}-methyl-amino)-ethyl]-3-methyl-1-[3-(2-oxo-pyrrolidin-1-yl)-propyl]-ureido}-propionic acid, Compound DG;

3-{(4-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetyl}-[1,4]diazepane-1-carbonyl)-[3-(2-oxo-pyrrolidin-1-yl)-propyl]-amino}-propionic acid, Compound DH;

3-[3-(2-{2-[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylamino}-ethyl)-1-methyl-ureido]-butyric acid, Compound DI;

3-[3-(3-{2-[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylamino}-propyl)-1-methyl-ureido]-butyric acid, Compound DJ;

3-[3-(3-{2-[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylamino}-2,2-dimethyl-propyl)-1-methyl-ureido]-butyric acid, Compound DK;

3-{3-[3-({[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetyl}-methyl-amino)-propyl]-1,3-dimethyl-ureido}-butyric acid, Compound DL;

3-{3-[2-({[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetyl}-methyl-amino)-ethyl]-1,3-dimethyl-ureido}-butyric acid, Compound DM;

3-[(4-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetyl}-[1,4]diazepane-1-carbonyl)-methyl-amino]-butyric acid, Compound DN;

3-[3-(3-{2-[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylamino}-propyl)-1-methyl-ureido]-2-methyl-propionic acid, Compound DO;

3-[3-(3-{2-[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylamino}-2,2-dimethyl-propyl)-1-methyl-ureido]-2-methyl-propionic acid, Compound DP;

3-{3-[3-({[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetyl}-methyl-amino)-propyl]-1,3-dimethyl-ureido}-2-methyl-propionic acid, Compound DQ;

3-{3-[2-({[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetyl}-methyl-amino)-ethyl]-1,3-dimethyl-ureido}-2-methyl-propionic acid, Compound DR;

3-[(4-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetyl}-[1,4]diazepane-1-carbonyl)-methyl-amino]-2-methyl-propionic acid, Compound DS;

3-[3-(3-{2-[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylamino}-propyl)-1-methyl-ureido]-propionic acid, Compound DT;

3-[3-(3-{2-[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylamino}-2,2-dimethyl-propyl)-1-methyl-ureido]-propionic acid,Compound DU;

3-{3-[3-({[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetyl}-methyl-amino)-propyl]-1,3-dimethyl-ureido}-propionic acid,Compound DV;

3-{3-[2-({[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetyl}-methyl-amino)-ethyl]-1,3-dimethyl-ureido}-propionic acid, Compound DW;

3-[(4-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetyl}-[1,4]diazepane-1-carbonyl)-methyl-amino]-propionic acid, Compound DX;

3-{3-(2-{2-[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylamino}-ethyl)-1-[3-(2-oxo-pyrrolidin-1-yl)-propyl]-ureido}-butyric acid, Compound DY;

3-{3-(3-{2-[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylamino}-propyl)-1-[3-(2-oxo-pyrrolidin-1-yl)-propyl]-ureido}-butyric acid, Compound DZ;

3-{3-(3-{2-[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylamino}-2,2-dimethyl-propyl)-1-[3-(2-oxo-pyrrolidin-1-yl)-propyl]-ureido}-butyric acid, Compound EA;

3-{3-[3-({[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetyl}-methyl-amino)-propyl]-3-methyl-1-[3-(2-oxo-pyrrolidin-1-yl)-propyl]-ureido}-butyric acid, Compound EB;

3-{3-[2-({[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetyl}-methyl-amino)-ethyl]-3-methyl-1-[3-(2-oxo-pyrrolidin-1-yl)-propyl]-ureido}-butyric acid, Compound EC;

3-{(4-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetyl}-[1,4]diazepane-1-carbonyl)-[3-(2-oxo-pyrrolidin-1-yl)-propyl]-amino}-butyric acid, Compound ED;

3-{3-(2-{3-[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-propionylamino}-ethyl)-1-[3-(2-oxo-pyrrolidin-1-yl)-propyl]-ureido}-propionic acid, Compound EE;

3-{3-(3-{3-[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-propionylamino}-propyl)-1-[3-(2-oxo-pyrrolidin-1-yl)-propyl]-ureido}-propionic acid, Compound EF;

3-{3-(3-{3-[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-propionylamino}-2,2-dimethyl-propyl)-1-[3-(2-oxo-pyrrolidin-1-yl)-propyl]-ureido}-propionic acid, Compound EG;

3-{3-[3-({3-[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-propionyl}-methyl-amino)-propyl]-3-methyl-1-[3-(2-oxo-pyrrolidin-1-yl)-propyl]-ureido}-propionic acid, Compound EH;

3-{3-[2-({3-[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-propionyl}-methyl-amino)-ethyl]-3-methyl-1-[3-(2-oxo-pyrrolidin-1-yl)-propyl]-ureido}-propionic acid, Compound EI;

3-{(4-{3-[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-propionyl}-[1,4]diazepane-1-carbonyl)-[3-(2-oxo-pyrrolidin-1-yl)-propyl]-amino}-propionic acid,Compound EJ;

3-[3-(2-{3-[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-propionylamino}-ethyl)-1-methyl-ureido]-butyric acid,Compound EK;

3-[3-(3-{3-[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-propionylamino}-propyl)-1-methyl-ureido]-butyric acid, Compound EL;

3-[3-(3-{3-[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-propionylamino}-2,2-dimethyl-propyl)-1-methyl-ureido]-butyric acid, Compound EM;

3-{3-[3-({3-[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-propionyl}-methyl-amino)-propyl]-1,3-dimethyl-ureido}-butyric acid, Compound EN;

3-{3-[2-({3-[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-propionyl}-methyl-amino)-ethyl]-1,3-dimethyl-ureido}-butyric acid, Compound EO;

3-[(4-{3-[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-propionyl}-[1,4]diazepane-1-carbonyl)-methyl-amino]-butyric acid, Compound EP;

3-[3-(2-{3-[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-propionylamino}-ethyl)-1-methyl-ureido]-2-methyl-propionic acid, Compound EQ;

3-[3-(3-{3-[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-propionylamino}-propyl)-1-methyl-ureido]-2-methyl-propionic acid, Compound ER;

3-[3-(3-{3-[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-propionylamino}-2,2-dimethyl-propyl)-1-methyl-ureido]-2-methyl-propionic acid, Compound ES;

3-{3-[3-({3-[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-propionyl}-methyl-amino)-propyl]-1,3-dimethyl-ureido}-2-methyl-propionic acid, Compound ET;

3-{3-[2-({3-[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-propionyl}-methyl-amino)-ethyl]-1,3-dimethyl-ureido}-2-methyl-propionic acid, Compound EU;

3-[(4-{3-[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-propionyl}-[1,4]diazepane-1-carbonyl)-methyl-amino]-2-methyl-propionic acid, Compound EV;

3-{3-(2-{3-[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-propionylamino}-ethyl)-1-[3-(2-oxo-pyrrolidin-1-yl)-propyl]-ureido}-butyric acid, Compound EW;

3-{3-(3-{3-[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-propionylamino}-propyl)-1-[3-(2-oxo-pyrrolidin-1-yl)-propyl]-ureido}-butyric acid, Compound EX;

3-{3-(3-{3-[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-propionylamino}-2,2-dimethyl-propyl)-1-[3-(2-oxo-pyrrolidin-1-yl)-propyl]-ureido}-butyric acid, Compound EYX;

3-{3-[3-({3-[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-propionyl}-methyl-amino)-propyl]-3-methyl-1-[3-(2-oxo-pyrrolidin-1-yl)-propyl]-ureido}-butyric acid, Compound EZ;

(R)-3-[(4-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetyl}-[1,4]diazepane-1-carbonyl)-amino]-butyric acid, Compound FA;

(S)-3-[(4-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetyl}-[1,4]diazepane-1-carbonyl)-amino]-butyric acid, Compound FB;

2-[(4-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetyl}-[1,4]diazepane-1-carbonyl)-amino]-succinamic acid, Compound FC;

3-[(4-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetyl}-[1,4]diazepane-1-carbonyl)-amino]-succinamic acid, Compound FD;

2-[(4-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetyl}-[1,4]diazepane-1-carbonyl)-amino]-succinic acid, Compound FE;

3-[(4-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetyl}-[1,4]diazepane-1-carbonyl)-amino]-2-methyl-propionic acid, Compound FF;

3-[(4-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetyl}-[1,4]diazepane-1-carbonyl)-amino]-propionic acid, Compound FG;

3-{3-[2-({[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetyl}-methyl-amino)-ethyl]-3-methyl-ureido}-butyric acid, Compound FH;

3-{3-[2-({[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetyl}-methyl-amino)-ethyl]-3-methyl-ureido}-butyric acid, Compound FI;

2-{3-[2-({[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetyl}-methyl-amino)-ethyl]-3-methyl-ureido}-succinamic acid, Compound FJ;

3-{3-[2-({[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetyl}-methyl-amino)-ethyl]-3-methyl-ureido}-succinamic acid, Compound FK;

2-{3-[2-({[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetyl}-methyl-amino)-ethyl]-3-methyl-ureido}-succinic acid, Compound FL;

3-{3-[2-({[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetyl}-methyl-amino)-ethyl]-3-methyl-ureido}-2-methyl-propionic acid, Compound FM;

3-{3-[2-({[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetyl}-methyl-amino)-ethyl]-3-methyl-ureido}-propionic acid, Compound FN;

3-{3-[3-({[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetyl}-methyl-amino)-propyl]-3-methyl-ureido}-butyric acid, Compound FO;

3-{3-[3-({[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetyl}-methyl-amino)-propyl]-3-methyl-ureido}-butyric acid, Compound FP;

2-{3-[3-({[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetyl}-methyl-amino)-propyl]-3-methyl-ureido}-succinamic acid, Compound FQR;

3-{3-[3-({[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetyl}-methyl-amino)-propyl]-3-methyl-ureido}-succinamic acid, Compound FR;

2-{3-[3-({[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetyl}-methyl-amino)-propyl]-3-methyl-ureido}-succinic acid, Compound FS;

3-{3-[3-({[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetyl}-methyl-amino)-propyl]-3-methyl-ureido}-2-methyl-propionic acid, Compound FT;

3-[3-(3-{2-[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylamino}-2,2-dimethyl-propyl)-ureido]-butyric acid, Compound FU;

3-[3-(3-{2-[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylamino}-2,2-dimethyl-propyl)-ureido]-butyric acid, Compound FV;

2-[3-(3-{2-[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylamino}-2,2-dimethyl-propyl)-ureido]-succinamic acid, Compound FW;

3-[3-(3-{2-[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylamino}-2,2-dimethyl-propyl)-ureido]-succinamic acid, Compound FX;

2-[3-(3-{2-[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylamino}-2,2-dimethyl-propyl)-ureido]-succinic acid, Compound FY;

3-[3-(3-{2-[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylamino}-2,2-dimethyl-propyl)-ureido]-2-methyl-propionic acid, Compound FZ;

3-[3-(3-{2-[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylamino}-2,2-dimethyl-propyl)-ureido]-propionic acid, Compound GA;

3-[3-(3-{2-[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylamino}-propyl)-ureido]-butyric acid, Compound GB;

3-[3-(3-{2-[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylamino}-propyl)-ureido]-butyric acid, Compound GC;

2-[3-(3-{2-[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylamino}-propyl)-ureido]-succinamic acid, Compound GD;

3-[3-(3-{2-[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylamino}-propyl)-ureido]-succinamic acid, Compound GE;

2-[3-(3-{2-[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylamino}-propyl)-ureido]-succinic acid, Compound GF;

3-[3-(3-{2-[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylamino}-propyl)-ureido]-2-methyl-propionic acid, Compound GG;

3-[3-(3-{2-[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylamino}-propyl)-ureido]-propionic acid, Compound GH;

3-[(4-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetyl}-piperazine-1-carbonyl)-amino]-butyric acid,Compound GI;

3-[(4-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetyl}-piperazine-1-carbonyl)-amino]-butyric acid,Compound GJ;

2-[(4-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetyl}-piperazine-1-carbonyl)-amino]-succinamic acid, Compound GK;

3-[(4-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetyl}-piperazine-1-carbonyl)-amino]-succinamic acid,Compound GL;

2-[(4-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetyl}-piperazine-1-carbonyl)-amino]-succinic acid, Compound GM;

3-[(4-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetyl}-piperazine-1-carbonyl)-amino]-2-methyl-propionic acid, Compound GN;

3-[(4-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetyl}-piperazine-1-carbonyl)-amino]-propionic acid, Compound GO;

3-[(4-{3-[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-propionyl}-[1,4]diazepane-1-carbonyl)-amino]-butyric acid, Compound GP;

3-[(4-{3-[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-propionyl}-[1,4]diazepane-1-carbonyl)-amino]-butyric acid, Compound GQ;

2-[(4-{3-[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-propionyl}-[1,4]diazepane-1-carbonyl)-amino]-succinamic acid,Compound GR;

3-[(4-{3-[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-propionyl}-[1,4]diazepane-1-carbonyl)-amino]-succinamic acid,Compound GS;

2-[(4-{3-[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-propionyl}-[1,4]diazepane-1-carbonyl)-amino]-succinic acid, Compound GT;

3-[(4-{3-[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-propionyl}-[1,4]diazepane-1-carbonyl)-amino]-2-methyl-propionic acid, Compound GU;

3-[(4-{3-[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-propionyl}-[1,4]diazepane-1-carbonyl)-amino]-propionic acid, Compound GV;

3-{3-[2-({3-[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-propionyl}-methyl-amino)-ethyl]-3-methyl-ureido}-butyric acid, Compound GW;

3-{3-[2-({3-[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-propionyl}-methyl-amino)-ethyl]-3-methyl-ureido}-butyric acid, Compound GX;

2-{3-[2-({3-[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-propionyl}-methyl-amino)-ethyl]-3-methyl-ureido}-succinamic acid, Compound GY;

3-{3-[2-({3-[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-propionyl}-methyl-amino)-ethyl]-3-methyl-ureido}-succinamic acid, Compound GZ;

2-{3-[2-({3-[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-propionyl}-methyl-amino)-ethyl]-3-methyl-ureido}-succinic acid, Compound HA;

3-{3-[2-({3-[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-propionyl}-methyl-amino)-ethyl]-3-methyl-ureido}-2-methyl-propionic acid, Compound HB;

3-{3-[2-({3-[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-propionyl}-methyl-amino)-ethyl]-3-methyl-ureido}-propionic acid, Compound HC;

3-{3-[3-({3-[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-propionyl}-methyl-amino)-propyl]-3-methyl-ureido}-butyric acid, Compound HD;

3-{3-[3-({3-[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-propionyl}-methyl-amino)-propyl]-3-methyl-ureido}-butyric acid, Compound HE;

2-{3-[3-({3-[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-propionyl}-methyl-amino)-propyl]-3-methyl-ureido}-succinamic acid, Compound HF;

3-{3-[3-({3-[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-propionyl}-methyl-amino)-propyl]-3-methyl-ureido}-succinamic acid, Compound HG;

2-{3-[3-({3-[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-propionyl}-methyl-amino)-propyl]-3-methyl-ureido}-succinic acid, Compound HH;

3-{3-[3-({3-[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-propionyl}-methyl-amino)-propyl]-3-methyl-ureido}-2-methyl-propionic acid, Compound HI;

3-{3-[3-({3-[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-propionyl}-methyl-amino)-propyl]-3-methyl-ureido}-propionic acid, Compound HJ;

3-[3-(3-{3-[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-propionylamino}-2,2-dimethyl-propyl)-ureido]-butyric acid, Compound HK;

3-[3-(3-{3-[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-propionylamino}-2,2-dimethyl-propyl)-ureido]-butyric acid, Compound HL;

2-[3-(3-{3-[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-propionylamino}-2,2-dimethyl-propyl)-ureido]-succinamic acid, Compound HM;

3-[3-(3-{3-[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-propionylamino}-2,2-dimethyl-propyl)-ureido]-succinamic acid, Compound HN;

3-[3-(3-{3-[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-propionylamino}-2,2-dimethyl-propyl)-ureido]-2-methyl-propionic acid, Compound HO;

3-[3-(3-{3-[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-propionylamino}-2,2-dimethyl-propyl)-ureido]-propionic acid, Compound HP;

3-[3-(3-{3-[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-propionylamino}-propyl)-ureido]-butyric acid, Compound HQ;

3-[3-(3-{3-[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-propionylamino}-propyl)-ureido]-butyric acid, Compound HR;

3-[3-(3-{3-[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-propionylamino}-propyl)-ureido]-succinamic acid, Compound HS;

2-[3-(3-{3-[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-propionylamino}-propyl)-ureido]-succinic acid, Compound HT;

3-[3-(3-{3-[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-propionylamino}-propyl)-ureido]-2-methyl-propionic acid, Compound HU;

3-[3-(3-{3-[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-propionylamino}-propyl)-ureido]-propionic acid, Compound HV;

3-[(4-{3-[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-propionyl}-piperazine-1-carbonyl)-amino]-butyric acid, Compound HW;

3-[(4-{3-[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-propionyl}-piperazine-1-carbonyl)-amino]-butyric acid, Compound HX;

2-[(4-{3-[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-propionyl}-piperazine-1-carbonyl)-amino]-succinamic acid, Compound HY;

3-[(4-{3-[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-propionyl}-piperazine-1-carbonyl)-amino]-succinamic acid, Compound HZ;

2-[(4-{3-[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-propionyl}-piperazine-1-carbonyl)-amino]-succinic acid, Compound IA;

3-[(4-{3-[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-propionyl}-piperazine-1-carbonyl)-amino]-2-methyl-propionic acid, Compound IB;

3-{1-[2-(3,4-dimethoxy-phenyl)-ethyl]-3-[3-({[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetyl}-methyl-amino)-propyl]-3-methyl-ureido}-propionic acid, Compound IC;

3-{1-[3-(2-methoxy-phenoxy)-propyl]-3-[3-({[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetyl}-methyl-amino)-propyl]-3-methyl-ureido}-propionic acid, Compound ID;

3-{3-[3-({[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetyl}-methyl-amino)-propyl]-3-methyl-1-[3-(2-oxo-pyrrolidin-1-yl)-propyl]-ureido}-propionic acid, Compound IE;

3-{3-[3-({[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetyl}-methyl-amino)-propyl]-3-methyl-ureido}-2-methyl-propionic acid, Compound IF;

3-{3-[3-({[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetyl}-methyl-amino)-propyl]-1,3-dimethyl-ureido}-butyric acid, Compound IG;

3-{3-benzyl-3-[2-(benzyl-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetyl}-amino)-ethyl]-1-[2-(3,4-dimethoxy-phenyl)-ethyl]-ureido}-propionic acid, Compound IH;

3-{3-benzyl-3-[2-(benzyl-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetyl}-amino)-ethyl]-1-[3-(2-methoxy-phenoxy)-propyl]-ureido}-propionic acid, Compound IJ;

3-{3-benzyl-3-[2-(benzyl-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetyl}-amino)-ethyl]-ureido}-butyric acid, Compound IK;

3-{3-benzyl-3-[2-(benzyl-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetyl}-amino)-ethyl]-1-[3-(2-oxo-pyrrolidin-1-yl)-propyl]-ureido}-propionic acid, Compound IL;

3-{3-benzyl-3-[2-(benzyl-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetyl}-amino)-ethyl]-ureido}-2-methyl-propionic acid, Compound IM;

3-{3-benzyl-3-[2-(benzyl-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetyl}-amino)-ethyl]-1-methyl-ureido}-butyric acid, Compound IN;

3-{1-[2-(3,4-dimethoxy-phenyl)-ethyl]-3-isopropyl-3-[3-(isopropyl-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetyl}-amino)-propyl]-ureido}-propionic acid, Compound IO;

3-{3-isopropyl-3-[3-(isopropyl-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetyl}-amino)-propyl]-1-[3-(2-methoxy-phenoxy)-propyl]-ureido}-propionic acid, Compound IP;

3-{3-isopropyl-3-[3-(isopropyl-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetyl}-amino)-propyl]-ureido}-butyric acid, Compound IQ;

3-{3-isopropyl-3-[3-(isopropyl-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetyl}-amino)-propyl]-1-[3-(2-oxo-pyrrolidin-1-yl)-propyl]-ureido}-propionic acid, Compound IR;

3-{3-isopropyl-3-[3-(isopropyl-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetyl}-amino)-propyl]-ureido}-2-methyl-propionic acid, Compound IS;

3-{3-isopropyl-3-[3-(isopropyl-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetyl}-amino)-propyl]-1-methyl-ureido}-butyric acid, Compound IT;

3-{1-[2-(3,4-dimethoxy-phenyl)-ethyl]-3-isopropyl-3-[2-(isopropyl-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetyl}-amino)-ethyl]-ureido}-propionic acid, Compound IU;

3-{3-isopropyl-3-[2-(isopropyl-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetyl}-amino)-ethyl]-1-[3-(2-methoxy-phenoxy)-propyl]-ureido}-propionic acid, Compound IW;

3-{3-isopropyl-3-[2-(isopropyl-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetyl}-amino)-ethyl]-ureido}-butyric acid, Compound IY;

3-{3-isopropyl-3-[2-(isopropyl-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetyl}-amino)-ethyl]-1-[3-(2-oxo-pyrrolidin-1-yl)-propyl]-ureido}-propionic acid, Compound IZ;

3-{3-isopropyl-3-[2-(isopropyl-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetyl}-amino)-ethyl]-ureido}-2-methyl-propionic acid, Compound JA;

3-{3-isopropyl-3-[2-(isopropyl-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetyl}-amino)-ethyl]-1-methyl-ureido}-butyric acid, Compound JB;

3-{1-[2-(3,4-dimethoxy-phenyl)-ethyl]-3-ethyl-3-[4-(ethyl-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetyl}-amino)-but-2-enyl]-ureido}-propionic acid, Compound JC;

3-{3-ethyl-3-[4-(ethyl-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetyl}-amino)-but-2-enyl]-1-[3-(2-methoxy-phenoxy)-propyl]-ureido}-propionic acid, Compound JD;

3-{3-ethyl-3-[4-(ethyl-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetyl}-amino)-but-2-enyl]-1-[3-(2-oxo-pyrrolidin-1-yl)-propyl]-ureido}-propionic acid, Compound JE;

3-{3-ethyl-3-[4-(ethyl-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetyl}-amino)-but-2-enyl]-ureido}-2-methyl-propionic acid, Compound JF;

3-{3-ethyl-3-[4-(ethyl-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetyl}-amino)-but-2-enyl]-1-methyl-ureido}-butyric acid, Compound JG;

3-{3-ethyl-3-[4-(ethyl-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetyl}-amino)-but-2-ynyl]-ureido}-2-methyl-propionic acid, Compound JH;

1-(1-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetyl}-3-methyl-azetidin-3-ylcarbamoyl)-piperidine-3-carboxylic acid, Compound JI;

1-[(1-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetyl}-piperidin-4-ylmethyl)-carbamoyl]-piperidine-3-carboxylic acid, Compound JJ;

1-(1-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetyl}-azepan-3-ylcarbamoyl)-piperidine-3-carboxylic acid, Compound JK;

1-(1-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetyl}-pyrrolidin-3-ylcarbamoyl)-piperidine-3-carboxylic acid, Compound JL;

1-(1-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetyl}-piperidin-4-ylcarbamoyl)-piperidine-3-carboxylic acid, Compound JM;

1-[(1-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetyl}-piperidin-3-ylmethyl)-carbamoyl]-piperidine-3-carboxylic acid, Compound JN;

1-[(1-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetyl}-pyrrolidin-3-ylmethyl)-carbamoyl]-piperidine-3-carboxylic acid, Compound JO;

1-(1-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetyl}-3-methyl-azetidin-3-ylcarbamoyl)-piperidine-4-carboxylic acid, Compound JP;

1-[(1-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetyl}-piperidin-4-ylmethyl)-carbamoyl]-piperidine-4-carboxylic acid, Compound JQ;

1-(1-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetyl}-azepan-3-ylcarbamoyl)-piperidine-4-carboxylic acid, Compound JR;

1-(1-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetyl}-pyrrolidin-3-ylcarbamoyl)-piperidine-4-carboxylic acid, Compound JS;

1-(1-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetyl}-piperidin-4-ylcarbamoyl) -piperidine-4-carboxylic acid, Compound JT;

1-[(1-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetyl}-piperidin-3-ylmethyl)-carbamoyl]-piperidine-4-carboxylic acid, Compound JU;

1-[(1-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetyl}-pyrrolidin-3-ylmethyl)-carbamoyl]-piperidine-4-carboxylic acid, Compound JV;

3-[3-(1-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetyl}-3-methyl-azetidin-3-yl)-ureido]-pentanedioic acid, Compound JW;

3-[3-(1-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetyl}-piperidin-4-ylmethyl)-ureido]-pentanedioic acid, Compound JX;

3-[3-(1-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetyl}-azepan-3-yl)-ureido]-pentanedioic acid, Compound JY;

3-[3-(1-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetyl}-pyrrolidin-3-yl)-ureido]-pentanedioic acid, Compound JZ;

3-[3-(1-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetyl}-piperidin-4-yl)-ureido]-pentanedioic acid, Compound KA;

3-[3-(1-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetyl}-pyrrolidin-3-ylmethyl)-ureido]-pentanedioic acid, Compound KB;

{4-[3-(1-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetyl}-3-methyl-azetidin-3-yl)-ureido]-phenyl}-acetic acid, Compound KC;

{4-[3-(1-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetyl}-piperidin-4-ylmethyl)-ureido]-phenyl}-acetic acid, Compound KD;

{4-[3-(1-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetyl}-azepan-3-yl)-ureido]-phenyl}-acetic acid, Compound KE;

{4-[3-(1-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetyl}-pyrrolidin-3-yl)-ureido]-phenyl}-acetic acid, Compound KF;

{4-[3-(1-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetyl}-piperidin-4-yl)-ureido]-phenyl}-acetic acid, Compound KG;

{4-[3-(1-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetyl}-piperidin-3-ylmethyl)-ureido]-phenyl}-acetic acid, Compound KH;

{4-[3-(1-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetyl}-pyrrolidin-3-ylmethyl)-ureido]-phenyl}-acetic acid, Compound KI;

3-{[2-(3,4-dimethoxy-phenyl)-ethyl]-[4-({2-[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylamino}-methyl)-piperidine-1-carbonyl]-amino}-propionic acid, Compound KJ;

3-[[2-(3,4-dimethoxy-phenyl)-ethyl]-(3-{2-[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylamino}-pyrrolidine-1-carbonyl)-amino]-propionic acid, Compound KK;

3-[[2-(3,4-dimethoxy-phenyl)-ethyl]-(4-{2-[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylamino}-piperidine-1-carbonyl)-amino]-propionic acid, Compound KL;

3-{[2-(3,4-dimethoxy-phenyl)-ethyl]-[3-({2-[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylamino}-methyl)-piperidine-1-carbonyl]-amino}-propionic acid, Compound KM;

3-{[2-(3,4-dimethoxy-phenyl)-ethyl]-[3-({2-[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylamino}-methyl)-pyrrolidine-1-carbonyl]-amino}-propionic acid, Compound KN;

3-{[4-({2-[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylamino}-methyl)-piperidine-1-carbonyl]-[3-(methyl-phenyl-amino)-propyl]-amino}-propionic acid, Compound KO;

3-{(3-{2-[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylamino}-pyrrolidine-1-carbonyl)-[3-(methyl-phenyl-amino)-propyl]-amino}-propionic acid, Compound KP;

3-{(4-{2-[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylamino}-piperidine-1-carbonyl)-[3-(methyl-phenyl-amino)-propyl]-amino}-propionic acid, Compound KQ;

3-{[3-({2-[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylamino}-methyl)-piperidine-1-carbonyl]-[3-(methyl-phenyl-amino)-propyl]-amino}-propionic acid, Compound KR;

3-{[3-({2-[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylamino}-methyl)-pyrrolidine-1-carbonyl]-[3-(methyl-phenyl-amino)-propyl]-amino}-propionic acid, Compound KS;

3-[3-(3-{2-[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylamino}-propyl)-3-methyl-ureido]-propionic acid, Compound KT;

(R)-3-[3-(3-{2-[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylamino}-propyl)-3-methyl-ureido]-butyric acid, Compound KU;

(S)-3-[3-(3-{2-[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylamino}-propyl)-3-methyl-ureido]-butyric acid, Compound KV;

3-[3-(2-{2-[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylamino}-cyclohexyl)-ureido]-butyric acid, Compound KW;

(S)-3-[(4-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetyl}-[1,4]diazepane-1-carbonyl)-amino]-butyric acid, Compound KY;

(R)-3-[(4-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetyl}-[1,4]diazepane-1-carbonyl)-amino]-butyric acid, Compound KZ;

3-{3-[3-({[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetyl}-methyl-amino)-propyl]-3-methyl-1-[3-(2-oxo-pyrrolidin-1-yl)-propyl]-ureido}-propionic acid, Compound LA;

3-{3-(3-{2-[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylamino}-propyl)-1-[3-(2-oxo-pyrrolidin-1-yl)-propyl]-ureido}-propionic acid, Compound LB;

3-{1-[3-(2-methoxy-phenoxy)-propyl]-3-[3-({[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetyl}-methyl-amino)-propyl]-3-methyl-ureido}-propionic acid, Compound LC;

(1-{[3-({[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetyl}-methyl-amino)-propyl]-methyl-carbamoyl}-3-oxo-piperazin-2-yl)-acetic acid, Compound LD;

(1-{[3-({[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetyl}-methyl-amino)-propyl]-methyl-carbamoyl}-4-phenyl-piperazin-2-yl)-acetic acid, Compound LE;

3-[(4-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetyl}-[1,4]diazepane-1-carbonyl)-amino]-pentanedioic acid, Compound LF;

3-{3-[3-({[2-methoxy-3-(3-(2-methylphenyl)ureido)-phenyl]-acetyl}-methyl-amino)-propyl]-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl}-propionic acid, Compound LI;

[S]-1-(1-{[3-methoxy-4-(3-(2-methylphenyl)ureido)phenyl]acetyl}azapam-3-ylcarbamoyl)piperidine-4-carboxylic acid, Compound LJ;

[R]-1-(1-{[3-methoxy-4-(3-(2-methylphenyl)ureido)phenyl]acetyl}azapam-3-ylcarbamoyl)piperidine-4-carboxylic acid, Compound LK;

1-(4-{[3-methoxy-4-(3-o-tolylureido)phenyl]acetyl}-[1,4]-diazepane-1-carbonyl)piperidine-4-carboxylic acid, Compound LL;

3-{(4-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetyl}-[1,4]diazepane-1-carbonyl)-[3-(methyl-phenyl-amino)-propyl]-amino}-propionic acid, (Compound LM);

3-{3-[3-({[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetyl}-methyl-amino)-propyl]-3-methyl-1-[3-(methyl-phenyl-amino)-propyl]-ureido}-propionic acid, Compound LN;

3-[[2-(3,4-dimethoxy-phenyl)-ethyl]-(4-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetyl}-[1,4]diazepane-1-carbonyl)-amino]-propionic acid, Compound LO;

3-{1-[2-(3,4-dimethoxy-phenyl)-ethyl]-3-[3-({[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetyl}-methyl-amino)-propyl]-3-methyl-ureido}-propionic acid, Compound LP;

3-[1-[2-(3,4-dimethoxy-phenyl)-ethyl]-3-(3-{2-[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylamino}-propyl)-3-methyl-ureido]-propionic acid, Compound LQ;

(4-{2-[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylamino}-piperidin-1-yl)-acetic acid, Compound LR;

3-(4-{[4-(3-(2-methylphenyl)ureido)-phenyl]-acetyl}-piperazin-1-yl)-propionic acid, Compound LS;

3-(4-{[4-(3-(2-methylphenyl)ureido)-phenyl]-acetyl}-homopiperazin-1-yl)-propionic acid, Compound LT;

(4-{[4-(3-(2-methylphenyl)ureido)-phenyl]-acetyl}-piperazin-1-yl)-acetic acid, Compound LU;

(4-{[4-(3-(2-methylphenyl)ureido)-phenyl]-acetyl}-homopiperazin-1-yl)-acetic acid, Compound LV;

(3-{[4-(3-(2-methylphenyl)ureido)-phenyl]-acetyl}-homopiperazin-1-yl)-phenylacetic acid, Compound LW;

(4-{[4-(3-(2-methylphenyl)ureido)-phenyl]-acetyl}-piperazin-1-yl)-butyric acid, Compound LX;

(4-{[4-(3-(2-methylphenyl)ureido)-phenyl]-acetyl}-homopiperazin-1-yl)-butyric acid, Compound LY;

3-(4-{[4-(3-(2-methylphenyl)ureido)-phenyl]-acetylaminomethyl}-piperidin-1-yl)-propionic acid, Compound LZ;

3-(3-{[4-(3-(2-methylphenyl)ureido)-phenyl]-acetylamino}-pyrrolidin-1-yl)-propionic acid, Compound MA;

3-(4-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylaminomethyl}-piperidin-1-yl)-propionic acid, Compound MB;

(4-{[3-(3-(2-methylphenyl)ureido)-phenyl]-acetylaminomethyl}-piperidin-1-yl)-acetic acid, Compound MC;

(3-{[4-(3-(2-methylphenyl)ureido)-phenyl]-acetylamino}-pyrrolidin-1-yl)-acetic acid, Compound MD;

[3-{[4-(3-(2-methylphenyl)ureido)-phenyl]-acetylamino}-propyl]-methylamino-acetic acid, Compound ME;

(4-{[4-(3-(2-methylphenyl)ureido)-phenyl]-acetylaminomethyl}-piperidin-1-yl)-acetic acid, Compound MF;

[3-{3-[4-(3-(2-methylphenyl)ureido)-phenyl]-propionylamino}-propyl]-methylamino-acetic acid , Compound MG;

5-(4-{[3-methoxy-4-(3-o-tolyl-ureido)-phenyl]-acetyl}-[1,4]diazepan-1-yl)-3-methyl-5-oxo-pentanoic acid, Compound LG;

4-(4-{[3-methoxy-4-(3-o-tolyl-ureido)-phenyl]-acetyl}-[1,4]diazepan-1-yl)-4-oxo-butanoic acid, Compound MH;

4-(4-{[3-methoxy-4-(3-o-tolyl-ureido)-phenyl]-acetyl}-[1,4]diazepan-1-yl)-4-oxo-3,3-dimethylbutanoic acid, Compound MI;

4-(4-{[3-methoxy-4-(3-o-tolyl-ureido)-phenyl]-acetyl}-[1,4]diazepan-1-yl)-4-oxo-3-phenylbutanoic acid, Compound MJ;

4-(4-{[3-methoxy-4-(3-o-tolyl-ureido)-phenyl]-acetyl}-[1,4]diazepan-1-yl)-4-oxo-3-methylbutanoic acid, Compound MK;

4-(4-{[3-methoxy-4-(3-o-tolyl-ureido)-phenyl]-acetyl}-[1,4]diazepan-1-yl)-4-oxo-3-(carbobenzyloxy)-butanoic acid, Compound ML;

2-(4-{[3-methoxy-4-(3-o-tolyl-ureido)-phenyl]-acetyl}-[1,4]diazepan-1-carbonyl)-cyclohexane-carboxylic acid, Compound MM;

3-(4-{[3-methoxy-4-(3-o-tolyl-ureido)-phenyl]-acetyl}-[1,4]diazepan-1-carbonyl)-4,7,7-trimethylbicyclo[2.2.1]heptane-2-carboxylic acid, Compound MN;

5-(4-{[3-methoxy-4-(3-o-tolyl-ureido)-phenyl]-acetyl}-[1,4]diazepan-1-yl)-5-oxo-pentanoic acid, Compound MO;

5-(4-{[3-methoxy-4-(3-o-tolyl-ureido)-phenyl]-acetyl}-[1,4]diazepan-1-yl)-3-ethyl-3-methyl-5-oxo-pentanoic acid, Compound MP;

5-(4-{[3-methoxy-4-(3-o-tolyl-ureido)-phenyl]-acetyl}-[1,4]diazepan-1-yl)-5-oxo-2,2-dimethylpentanoic acid, Compound MQ;

5-(4-{[3-methoxy-4-(3-o-tolyl-ureido)-phenyl]-acetyl}-[1,4]diazepan-1-yl)-2-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-5-oxo-pentanoic acid, Compound MR;

5-(4-{[3-methoxy-4-(3-o-tolyl-ureido)-phenyl]-acetyl}-[1,4]diazepan-1-yl)-5-oxo-3-phenylpentanoic acid, Compound MS;

5-(4-{[3-methoxy-4-(3-o-tolyl-ureido)-phenyl]-acetyl}-[1,4]diazepan-1-yl)-3-ethyl-3,3-dimethyl-5-oxo-pentanoic acid, Compound MT;

2-[5-(4-{[3-methoxy-4-(3-o-tolyl-ureido)-phenyl]-acetyl}-[1,4]diazepan-1-yl)-2-oxo-ethyl]-benzoic acid, Compound MU;

4-(4-{3-[3-methoxy-4-(3-o-tolyl-ureido)-phenyl]-propionyl}-[1,4]diazepan-1-yl)-4-oxo-butanoic acid, Compound MV;

4-(4-{3-[3-methoxy-4-(3-o-tolyl-ureido)-phenyl]-propionyl}-[1,4]diazepan-1-yl)-4-oxo-3,3-dimethylbutanoic acid., Compound MW;

4-(4-{3-[3-methoxy-4-(3-o-tolyl-ureido)-phenyl]-propionyl}-[1,4]diazepan-1-yl)-4-oxo-3-phenylbutanoic acid, Compound MX;

4-(4-{3-[3-methoxy-4-(3-o-tolyl-ureido)-phenyl]-propionyl}-[1,4]diazepan-1-yl)-4-oxo-3-methylbutanoic acid, Compound MY;

4-(4-{3-[3-methoxy-4-(3-o-tolyl-ureido)-phenyl]-propionyl}-[1,4]diazepan-1-yl)-4-oxo-3-(carbobenzyloxy)-butanoic acid, Compound MZ;

2-(4-{3-[3-methoxy-4-(3-o-tolyl-ureido)-phenyl]-propionyl}-[1,4]diazepan-1-carbonyl)-cyclohexane-carboxylic acid, Compound NA;

3-(4-{3-[3-methoxy-4-(3-o-tolyl-ureido)-phenyl]-propionyl}-[1,4]diazepan-1-carbonyl)-4,7,7-trimethylbicyclo[2.2.1]heptane-2-carboxylic acid, Compound NB;

5-(4-{3-[3-methoxy-4-(3-o-tolyl-ureido)-phenyl]-propionyl}-[1,4]diazepan-1-yl)-5-oxo-pentanoic acid, Compound NC;

5-(4-{3-[3-methoxy-4-(3-o-tolyl-ureido)-phenyl]-propionyl}-[1,4]diazepan-1-yl)-3-methyl-5-oxo-pentanoic acid, Compound ND;

5-(4-{3-[3-methoxy-4-(3-o-tolyl-ureido)-phenyl]-propionyl}-[1,4]diazepan-1-yl)-3-ethyl-3-methyl-5-oxo-pentanoic acid, Compound NE;

5-(4-{3-[3-methoxy-4-(3-o-tolyl-ureido)-phenyl]-propionyl}-[1,4]diazepan-1-yl)-2,2-dimethyl-5-oxo-pentanoic acid, Compound NF;

5-(4-{3-[3-methoxy-4-(3-o-tolyl-ureido)-phenyl]-propionyl}-[1,4]diazepan-1-yl)-2-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-5-oxo-pentanoic acid, Compound NG;

5-(4-{3-[3-methoxy-4-(3-o-tolyl-ureido)-phenyl]-propionyl}-[1,4]diazepan-1-yl)-5-oxo-3-phenylpentanoic acid, Compound NH;

5-(4-{3-[3-methoxy-4-(3-o-tolyl-ureido)-phenyl]-propionyl}-[1,4]diazepan-1-yl)-3,3-dimethyl-5-oxo-pentanoic acid, Compound NI;

2-[5-(4-{3-[3-methoxy-4-(3-o-tolyl-ureido)-phenyl]-propionyl}-[1,4]diazepan-1-yl)-2-oxo-ethyl]-benzoic acid, Compound NJ;

2-benzyloxycarbonylamino-3-[4-({2-[3-methoxy-4-(3-o-tolyl-ureido)-phenyl]-acetylamino}-methyl)-piperidin-1-yl]-propionic acid, Compound NK;

5-[4-({2-[3-methoxy-4-(3-o-tolyl-ureido)-phenyl]-acetylamino}-methyl)-piperidin-1-yl]-5-oxo-pentanoic acid, Compound NL;

(*S*)-2-tert-Butoxycarbonylamino-5-[4-({2-[3-methoxy-4-(3-o-tolyl-ureido)-phenyl]-acetylamino}-methyl)-piperidin-1-yl]-5-oxo-pentanoic acid, Compound NM;

(*R*)-2-tert-butoxycarbonylamino-5-[4-({2-[3-methoxy-4-(3-o-tolyl-ureido)-phenyl]-acetylamino}-methyl)-piperidin-1-yl]-5-oxo-pentanoic acid, Compound NN;

3-{3-[3-({[2-o-tolylaminobenzoxazol-6-yl]-acetyl}-methyl-amino)-propyl]-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl}-propionic acid;

3-(4-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylaminomethyl}-piperidin-1-yl)-butyric acid;

3-(4-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylaminomethyl}-piperidin-1-yl)-3-phenylpropionic acid;

3-(4-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylaminomethyl}-piperidin-1-yl)-3-(3,4-dimethoxyphenyl)propionic acid;

2-(4-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylaminomethyl}-piperidin-1-yl)-acetic acid;

4-(4-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylaminomethyl}-piperidin-1-yl)-butyric acid;

4-(4-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylaminomethyl}-piperidin-1-yl)-3-methylbutyric acid;

3-(4-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylamino}-piperidin-1-yl)-propionic acid;

3-(4-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylamino}-piperidin-1-yl)-butyric acid;

3-(4-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylamino}-piperidin-1-yl)-3-phenylpropionic acid;

3-(4-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylamino}-piperidin-1-yl)-3-(3,4-dimethoxyphenyl)propionic acid;

3-(3-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylaminomethyl}-pyrrolidin-1-yl)-propionic acid;

3-(3-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylaminomethyl}-pyrrolidin-1-yl)-butyric acid;

3-(3-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylaminomethyl}-pyrrolidin-1-yl)-3-phenylpropionic acid;

3-(3-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylaminomethyl}-pyrrolidin-1-yl)3-(3,4-dimethoxyphenyl)propionic acid;

2-(3-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylaminomethyl}-pyrrolidin-1-yl)-acetic acid;

4-(3-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylaminomethyl}-pyrrolidin-1-yl)-butyric acid;

4-(3-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylaminomethyl}-pyrrolidin-1-yl)-3-methylbutyric acid;

3-(3-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylamino}-pyrrolidin-1-yl)-propionic acid;

3-(3-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylamino}-pyrrolidin-1-yl)-butyric acid;

3-(3-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylamino}-pyrrolidin-1-yl)-3-phenylpropionic acid;

3-(3-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylamino}-pyrrolidin-1-yl)3-(3,4-dimethoxyphenyl)propionic acid;

2-(3-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylamino}-pyrrolidin-1-yl)-acetic acid;

4-(3-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylamino}-pyrrolidin-1-yl)-butyric acid;

4-(3-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylamino}-pyrrolidin-1-yl)-3-methylbutyric acid;

3-(3-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylaminoethyl}-pyrrolidin-1-yl)-propionic acid;

3-(3-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylaminoethyl}-pyrrolidin-1-yl)-butyric acid;

3-(3-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylaminoethyl}-pyrrolidin-1-yl)-3-phenylpropionic acid;

3-(3-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylaminoethyl}-pyrrolidin-1-yl)3-(3,4-dimethoxyphenyl)propionic acid;

2-(3-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylaminoethyl}-pyrrolidin-1-yl)-acetic acid;

4-(3-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylaminoethyl}-pyrrolidin-1-yl)-butyric acid;

4-(3-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylaminoethyl}-pyrrolidin-1-yl)-3-methylbutyric acid;

3-(4-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylaminoethyl}-piperidin-1-yl)-propionic acid;

3-(4-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylaminoethyl}-piperidin-1-yl)-butyric acid;

3-(4-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylaminoethyl}-piperidin-1-yl)-3-phenylpropionic acid;

3-(4-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylaminoethyl}-piperidin-1-yl)3-(3,4-dimethoxyphenyl)propionic acid;

2-(4-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylaminoethyl}-piperidin-1-yl)-acetic acid;

4-(4-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylaminoethyl}-piperidin-1-yl)-butyric acid;

4-(4-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylaminoethyl}-piperidin-1-yl)-3-methylbutyric acid;

3-(4-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylaminomethyl}-azepin-1-yl)-propionic acid;

3-(4-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylaminomethyl}-azepin-1-yl)-butyric acid;

3-(4-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylaminomethyl}-azepin-1-yl)-3-phenylpropionic acid;

3-(4-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylaminomethyl}-azepin-1-yl)3-(3,4-dimethoxyphenyl)propionic acid;

2-(4-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylaminomethyl}-azepin-1-yl)-acetic acid;

4-(4-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylaminomethyl}-azepin-1-yl)-butyric acid;

4-(4-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylaminomethyl}-azepin-1-yl)-3-methylbutyric acid;

3-(3-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylaminomethyl}-azepin-1-yl)-propionic acid;

3-(3-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylaminomethyl}-azepin-1-yl)-butyric acid;

3-(3-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylaminomethyl}-azepin-1-yl)-3-phenylpropionic acid;

3-(3-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylaminomethyl}-azepin-1-yl)3-(3,4-dimethoxyphenyl)propionic acid;

2-(3-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylaminomethyl}-azepin-1-yl)-acetic acid;

4-(3-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylaminomethyl}-azepinin-1-yl)-butyric acid;

4-(3-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylaminomethyl}-azepin-1-yl)-3-methylbutyric acid;

2-(3-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylamino}-azepin-1-yl)-acetic acid;

3-(3-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylamino}-azepin-1-yl)-propionic acid;

3-(3-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylamino}-azepin-1-yl)-butyric acid;

3-(3-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylamino}-azepin-1-yl)-3-phenylpropionic acid;

3-(3-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylamino}-azepin-1-yl)-3-(3,4-dimethoxyphenyl)propionic acid;

3-(3-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylaminoethyl}-azepin-1-yl)-propionic acid;

3-(3-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylaminoethyl}-azepin-1-yl)-butyric acid;

3-(3-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylaminoethyl}-azepin-1-yl)-3-phenylpropionic acid;

3-(3-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylaminoethyl}-azepin-1-yl)3-(3,4-dimethoxyphenyl)propionic acid;

2-(3-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylaminoethyl}-azepin-1-yl)-acetic acid;

4-(3-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylaminoethyl}-azepin-1-yl)-butyric acid;

4-(3-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylaminoethyl}-azepin-1-yl)-3-methylbutyric acid;

2-(4-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylamino}-azepin-1-yl)-acetic acid;

3-(4-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylamino}-azepin-1-yl)-propionic acid;

3-(4-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylamino}-azepin-1-yl)-butyric acid;

3-(4-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylamino}-azepin-1-yl)-3-phenylpropionic acid;

3-(4-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylamino}-azepin-1-yl)-3-(3,4-dimethoxyphenyl)propionic acid;

3-(4-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylaminoethyl}-azepin-1-yl)-propionic acid;

3-(4-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylaminoethyl}-azepin-1-yl)-butyric acid;

3-(4-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylaminoethyl}-azepin-1-yl)-3-phenylpropionic acid;

3-(4-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylaminoethyl}-azepin-1-yl)3-(3,4-dimethoxyphenyl)propionic acid;

2-(4-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylaminoethyl}-azepin-1-yl)-acetic acid;

4-(4-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylaminoethyl}-azepin-1-yl)-butyric acid;

4-(4-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylaminoethyl}-azepin-1-yl)-3-methylbutyric acid;

3-(4-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetyl-(N-methyl)amino-methyl}-piperidin-1-yl)-propionic acid;

3-(4-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetyl-(N-methyl)amino-methyl}-piperidin-1-yl)-butyric acid;

3-(4-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetyl-(N-methyl)amino-methyl}piperidin-1-yl)-3-phenylpropionic acid;

3-(4-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetyl-(N-methyl)amino-methyl}piperidin-1-yl)-3-(3,4-dimethoxyphenyl)-propionic acid;

2-(4-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetyl-(N-methyl)amino-methyl}piperidin-1-yl)-acetic acid;

4-(4-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetyl-(N-methyl)amino-methyl}piperidin-1-yl)-butyric acid;

4-(4-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetyl-(N-methyl)amino-methyl}piperidin-1-yl)-3-methylbutyric acid;

3-(4-{1-([3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylamino)ethyl}-piperidin-1-yl)-propionic acid;

3-(4-{1-([3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylamino)ethyl}-piperidin-1-yl)-butyric acid;

3-(4-{1-([3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylamino)ethyl}-piperidin-1-yl)-3-phenylpropionic acid;

3-(4-{1-([3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylamino)ethyl}-piperidin-1-yl)3-(3,4-dimethoxyphenyl)propionic acid;

2-(4-{1-([3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylamino)ethyl}-piperidin-1-yl)-acetic acid;

4-(4-{1-([3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylamino)ethyl}-piperidin-1-yl)-butyric acid;

4-(4-{1-([3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylamino)ethyl}-piperidin-1-yl)-3-methylbutyric acid;

(4-{[4-methoxy-3-(3-(2-methylphenyl)ureido)-phenyl]-acetylaminomethyl}-piperidin-1-yl)-acetic acid;

(4-{[2-methoxy-3-(3-(2-methylphenyl)ureido)-phenyl]-acetylaminomethyl}-piperidin-1-yl)-acetic acid;

(4-{[3-(3-(2-methylphenyl)ureido)-phenyl]-acetylaminomethyl}-piperidin-1-yl)-acetic acid;

(4-{[3-(3-(2-methylphenyl)ureido)-phenyl]-acetyl-(N-methyl)aminomethyl}-piperidin-1-yl)-acetic acid;

(4-{[3-(3-(2-methylphenyl)ureido)-phenyl]-acetylaminomethyl}-azepin-1-yl)-acetic acid;

(3-{[3-(3-(2-methylphenyl)ureido)-phenyl]-acetylaminomethyl}-azepin-1-yl)-acetic acid;

(4-{[3-(3-(2-methylphenyl)ureido)-phenyl]-acetylamino}-azepin-1-yl)-acetic acid;

(3-{[3-(3-(2-methylphenyl)ureido)-phenyl]-acetylamino}-azepin-1-yl)-acetic acid;

3-([3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylaminoethylamino)-propionic acid;

3-([3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylaminoethylamino)-butyric acid;

3-([3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylaminoethylamino)-3-phenylpropionic acid;

3-([3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylaminoethylamino)3-(3,4-dimethoxyphenyl)propionic acid;

2-([3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylaminoethylamino)acetic acid;

4-([3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylaminoethylamino)-butyric acid;

4-([3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylaminoethylamino)-3-methylbutyric acid;

3-(N-methyl-([3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylaminoethyl)-amino)-propionic acid;

3-(N-methyl-([3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylaminoethyl)-amino)-butyric acid;

3-(N-methyl-([3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylaminoethyl)-amino)-3-phenylpropionic acid;

3-(N-methyl-([3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylaminoethyl)-amino)3-(3,4-dimethoxyphenyl)propionic acid;

2-(N-methyl-([3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylaminoethyl)-amino)-acetic acid;

4-(N-methyl-([3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylaminoethyl)-amino)-butyric acid;

4-(N-methyl-([3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylaminoethyl-amino)-3-methylbutyric acid;

3-(N-benzyl-([3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylaminoethyl)-amino)-propionic acid;

3-(N-(3,4-dimethoxy)benzyl-([3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylaminoethyl)amino)-propionic acid;

3-(N-(3-imidazol-1-yl)propyl([3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylaminoethyl)amino)-propionic acid;

3-(N-(3-(pyrrolidin-2-one)propyl(3,4-dimethoxy)benzyl-([3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylaminoethyl)amino)propionic acid;

3-(N-benzyl-([3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylaminopropyl)-amino)-propionic acid;

3-(N-(3,4-dimethoxy)benzyl-([3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]acetylaminopropyl)amino)-propionic acid;

3-(N-(3-imidazol-1-yl)propyl([3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylaminopropyl)amino)-propionic acid;

3-(N-(3-(pyrrolidin-2-one)propyl(3,4-dimethoxy)benzyl-([3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylaminopropyl)amino)-propionic acid;

3-(4-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-propionylaminomethyl}-piperidin-1-yl)-propionic acid;

3-(4-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-propionylaminomethyl}-piperidin-1-yl)-butyric acid;

3-(4-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-propionylaminomethyl}-piperidin-1-yl)-3-phenylpropionic acid;

3-(4-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-propionylaminomethyl}-piperidin-1-yl)3-(3,4-dimethoxyphenyl)propionic acid;

2-(4-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-propionylaminomethyl}-piperidin-1-yl)-acetic acid;

4-(4-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-propionylaminomethyl}-piperidin-1-yl)-butyric acid;

4-(4-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-propionylaminomethyl}-piperidin-1-yl)-3-methylbutyric acid;

2-(4-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-propionylamino}-piperidin-1-yl)-acetic acid;

3-(4-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-propionylamino}-piperidin-1-yl)-propionic acid;

3-(4-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-propionylamino}-piperidin-1-yl)-butyric acid;

3-(4-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-propionylamino}-piperidin-1-yl)-3-phenylpropionic acid;

3-(4-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-propionylamino}-piperidin-1-yl)-3-(3,4-dimethoxyphenyl)propionic acid;

3-(N-benzyl-([3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-propionylaminoethyl)-amino)-propionic acid;

3-(N-(3,4-dimethoxy)benzyl-([3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-propionylaminoethyl)-amino)-propionic acid;

3-(N-(3-imidazol-1-yl)propyl-([3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-propionylaminoethyl)-amino)-propionic acid;

3-(N-(3-(pyrrolidin-2-one)propyl-(3,4-dimethoxy)benzyl-([3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-propionylaminoethyl)-amino)-propionic acid;

3-(N-benzyl-([3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-propionylaminopropyl)-amino)-propionic acid;

3-(N-(3,4-dimethoxy)benzyl-([3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-propionylylaminopropyl)-amino)-propionic acid;

3-(N-(3-imidazol-1-yl)propyl-([3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-propionylaminopropyl)-amino)-propionic acid;

3-(N-(3-(pyrrolidin-2-one)propyl-(3,4-dimethoxy)benzyl-([3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-propionylaminopropyl)-amino)-propionic acid;

3-(N-methyl-([3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylaminopropyl)-amino)-propionic acid;

3-(N-methyl-([3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylaminopropyl)-amino)-butyric acid;

3-(N-methyl-([3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylaminopropyl)-amino)-3-phenylpropionic acid;

3-(N-methyl-([3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylaminopropyl)-amino)-3-(3,4-dimethoxyphenyl)propionic acid;

2-(N-methyl-([3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylaminopropyl)-amino)-acetic acid;

4-(N-methyl-([3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylaminopropyl)-amino)-butyric acid;

4-(N-methyl-([3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylaminopropylamino)-3-methylbutyric acid;

3-([3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylaminopropylamino)-propionic acid;

3-([3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylaminopropylamino)-butyric acid;

3-([3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylaminopropylamino)-3-phenylpropionic acid;

3-([3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylaminopropylamino)3-(3,4-dimethoxyphenyl)propionic acid;

2-([3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylaminopropylamino)-acetic acid;

4-([3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylaminopropylamino)-butyric acid;

4-([3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylaminopropylamino)-3-methylbutyric acid;

and their prodrugs, and pharmaceutically acceptable salts and solvates (e.g. hydrates) of such compounds and their prodrugs.

Preferred compounds of the invention include:

3-{[(4-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetyl}-homopiperazin-1-yl)-carbonyl]-[3-(2-oxo-pyrrolidin-1-yl)-propyl]-amino}-propionic acid, Compound A;

3-{[(4-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetyl}-homopiperazin-1-yl)-carbonyl]-amino}-butanoic acid, Compound BJ;

(R)-3-[3-(3-{2-[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylamino}-propyl)-3-methyl-ureido]-butyric acid, Compound KU;

(S)-3-[(4-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetyl}-[1,4]diazepane-1-carbonyl)-amino]-butyric acid, Compound KY;

(R)-3-[(4-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetyl}-[1,4]diazepane-1-carbonyl)-amino]-butyric acid, Compound KZ;

3-{3-[3-({[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetyl}-methyl-amino)-propyl]-3-methyl-1-[3-(2-oxo-pyrrolidin-1-yl)-propyl]-ureido}-propionic acid, Compound LA;

3-{1-[3-(2-methoxy-phenoxy)-propyl]-3-[3-({[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetyl}-methyl-amino)-propyl]-3-methyl-ureido}-propionic acid, Compound LC;

3-{1-[2-(3,4-dimethoxy-phenyl)-ethyl]-3-[3-({[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetyl}-methyl-amino)-propyl]-3-methyl-ureido}-propionic acid, Compound LP;

3-{3-[3-({[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetyl}-methyl-amino)-propyl]-3-methyl-1-[3-(methyl-phenyl-amino)-propyl]-ureido}-propionic acid, Compound LN;

3-{3-[3-({[2-methoxy-3-(3-(2-methylphenyl)ureido)-phenyl]-acetyl}-methyl-amino)-propyl]-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl}-propionic acid, Compound LI;

3-{(4-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetyl}-[1,4]diazepane-1-carbonyl)-[3-(methyl-phenyl-amino)-propyl]-amino}-propionic acid, (Compound LM);

3-(4-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylaminomethyl}-piperidin-1-yl)-propionic acid, Compound MB;

2-benzyloxycarbonylamino-3-[4-({2-[3-methoxy-4-(3-o-tolyl-ureido)-phenyl]-acetylamino}-methyl)-piperidin-1-yl]-propionic acid, Compound NK;

5-[4-({2-[3-methoxy-4-(3-o-tolyl-ureido)-phenyl]-acetylamino}-methyl)-piperidin-1-yl]-5-oxo-pentanoic acid; Compound NL;

and their prodrugs, and pharmaceutically acceptable salts and solvates (e.g. hydrates) of such compounds and their prodrugs.

The compounds of the invention exhibit useful pharmacological activity and accordingly are incorporated into pharmaceutical compositions and used in the treatment of patients suffering from certain medical disorders. The present invention thus provides, according to a further aspect, compounds of the invention and compositions containing compounds of the invention for use in therapy.

Compounds within the scope of the present invention block the interaction of the ligand VCAM-1 to its integrin receptor VLA-4 ($\alpha 4\beta 1$) according to tests described in the literature and described in vitro and in vivo procedures hereinafter, and which tests results are believed to

correlate to pharmacological activity in humans and other mammals. Thus, in a further embodiment, the present invention provides compounds of the invention and compositions containing compounds of the invention for use in the treatment of a patient suffering from, or subject to, conditions which can be ameliorated by the administration of an inhibitor of $\alpha 4\beta 1$ mediated cell adhesion. For example, compounds of the present invention are useful in the treatment of inflammatory diseases, for example joint inflammation, including arthritis, rheumatoid arthritis and other arthritic conditions such as rheumatoid spondylitis, gouty arthritis, traumatic arthritis, rubella arthritis, psoriatic arthritis and osteoarthritis. Additionally, the compounds are useful in the treatment of acute synovitis, autoimmune diabetes, autoimmune encephalomyelitis, collitis, atherosclerosis, peripheral vascular disease, cardiovascular disease, multiple sclerosis, asthma, psoriasis restenosis, myocarditis, inflammatory bowel disease and melanoma cell division in metastasis.

A special embodiment of the therapeutic methods of the present invention is the treating of asthma.

Another special embodiment of the therapeutic methods of the present invention is the treating of joint inflammation.

Another special embodiment of the therapeutic methods of the present invention is the treating of inflammatory bowel disease.

According to a further feature of the invention there is provided a method for the treatment of a human or animal patient suffering from, or subject to, conditions which can be ameliorated by the administration of an inhibitor of the interaction of the ligand VCAM-1 to its integrin receptor VLA-4 ($\alpha 4\beta 1$), for example conditions as hereinbefore described, which comprises the administration to the patient of an effective amount of compound of the invention or a composition containing a compound of the invention. "Effective amount" is meant to describe an amount of compound of the present invention effective in inhibiting the interaction of the ligand VCAM-1 to its integrin receptor VLA-4 ($\alpha 4\beta 1$), and thus producing the desired therapeutic effect.

References herein to treatment should be understood to include prophylactic therapy as well as treatment of established conditions.

The present invention also includes within its scope pharmaceutical compositions comprising at least one of the compounds of the invention in association with a pharmaceutically acceptable carrier or excipient.

Compounds of the invention may be administered by any suitable means. In practice compounds of the present invention may generally be administered parenterally, topically, rectally, orally or by inhalation, especially by the oral route.

Compositions according to the invention may be prepared according to the customary methods, using one or more pharmaceutically acceptable adjuvants or excipients. The adjuvants comprise, inter alia, diluents, sterile aqueous media and the various non-toxic organic solvents. The compositions may be presented in the form of tablets, pills, granules, powders, aqueous solutions or suspensions, injectable solutions, elixirs or syrups, and can contain one or more agents chosen from the group comprising sweeteners, flavourings, colourings, or stabilisers in order to obtain pharmaceutically acceptable preparations. The choice of vehicle and the content of active substance in the vehicle are generally determined in accordance with the solubility and chemical properties of the active compound, the particular mode of administration and the provisions to be observed in pharmaceutical practice. For example, excipients such as lactose, sodium citrate, calcium carbonate, dicalcium phosphate and disintegrating agents such as starch, alginic acids and certain complex silicates combined with lubricants such as magnesium stearate, sodium lauryl sulphate and talc may be used for preparing tablets. To prepare a capsule, it is advantageous to use lactose and high molecular weight polyethylene glycols. When aqueous suspensions are used they can contain emulsifying agents or agents which facilitate suspension. Diluents such as sucrose, ethanol, polyethylene glycol, propylene glycol, glycerol and chloroform or mixtures thereof may also be used.

For parenteral administration, emulsions, suspensions or solutions of the products according to the invention in vegetable oil, for example sesame oil, groundnut oil or olive oil, or aqueous-organic solutions such as water and propylene glycol, injectable organic esters such as ethyl oleate, as well as sterile aqueous solutions of the pharmaceutically acceptable salts, are used. The solutions of the salts of the products according to the invention are especially useful for administration by intramuscular or subcutaneous injection. The aqueous solutions, also comprising solutions of the salts in pure distilled water, may be used for intravenous administration with the proviso that their pH is suitably adjusted, that they are judiciously buffered and rendered isotonic with a sufficient quantity of glucose or sodium chloride and that they are sterilised by heating, irradiation or microfiltration.

For topical administration, gels (water or alcohol based), creams or ointments containing compounds of the invention may be used. Compounds of the invention may also be incorporated in a gel or matrix base for application in a patch, which would allow a controlled release of compound through the transdermal barrier.

For administration by inhalation compounds of the invention may be dissolved or suspended in a suitable carrier for use in a nebuliser or a suspension or solution aerosol, or may be absorbed or adsorbed onto a suitable solid carrier for use in a dry powder inhaler.

Solid compositions for rectal administration include suppositories formulated in accordance with known methods and containing at least one compound of the invention.

The percentage of active ingredient in the compositions of the invention may be varied, it being necessary that it should constitute a proportion such that a suitable dosage shall be obtained. Obviously, several unit dosage forms may be administered at about the same time. The dose employed will be determined by the physician, and depends upon the desired therapeutic effect, the route of administration and the duration of the treatment, and the condition of the patient. In the adult, the doses are generally from about 0.001 to about 50, preferably about 0.001 to about 5, mg/kg body weight per day by inhalation, from about 0.01 to about 100, preferably 0.1 to 70, more especially 0.5 to 10, mg/kg body weight per day by oral administration, and from about 0.001 to about 10, preferably 0.01 to 1, mg/kg body weight per day by intravenous administration. In each particular case, the doses will be determined in accordance with the factors distinctive to the subject to be treated, such as age, weight, general state of health and other characteristics which can influence the efficacy of the medicinal product.

The compounds according to the invention may be administered as frequently as necessary in order to obtain the desired therapeutic effect. Some patients may respond rapidly to a higher or lower dose and may find much weaker maintenance doses adequate. For other patients, it may be necessary to have long-term treatments at the rate of 1 to 4 doses per day, in accordance with the physiological requirements of each particular patient. Generally, the active product may be administered orally 1 to 4 times per day. Of course, for some patients, it will be necessary to prescribe not more than one or two doses per day.

Compounds of the invention may be prepared by the application or adaptation of known methods, by which is meant methods used heretofore or described in the literature, for example

those described by R.C.Larock in Comprehensive Organic Transformations, VCH publishers, 1989.

In the reactions described hereinafter it may be necessary to protect reactive functional groups, for example hydroxy, amino, imino, thio or carboxy groups, where these are desired in the final product, to avoid their unwanted participation in the reactions. Conventional protecting groups may be used in accordance with standard practice, for examples see T.W. Green and P.G.M. Wuts in "Protective Groups in Organic Chemistry" John Wiley and Sons, 1991.

Thus, for example, compounds of formula (I) wherein $R^1$, $R^2$, $R^3$, $R^4$, $L^1$, $L^2$ and m are as hereinbefore defined, and Y is carboxy may be prepared by hydrolysis of esters of formula (I), wherein $R^1$, $R^2$, $R^3$, $R^4$, $L^1$, $L^2$ and m are as hereinbefore defined, and Y is $-CO_2R^{15}$ (in which $R^{15}$ is alkyl, alkenyl, aryl or arylalkyl). The hydrolysis may conveniently be carried out by alkaline hydrolysis using a base, such as an alkali metal hydroxide, e.g. lithium hydroxide, or an alkali metal carbonate, e.g. potassium carbonate, in the presence of an aqueous/organic solvent mixture, using organic solvents such as dioxan, tetrahydrofuran or methanol, at a temperature from about ambient to about reflux. The hydrolysis of the esters may also be carried out by acid hydrolysis using an inorganic acid, such as hydrochloric acid, in the presence of an aqueous/inert organic solvent mixture, using organic solvents such as dioxan or tetrahydrofuran, at a temperature from about 50°C to about 80°C.

As another example compounds of formula (I) wherein $R^1$, $R^2$, $R^3$, $R^4$, $L^1$, $L^2$ and m are as hereinbefore defined, and Y is carboxy may be prepared by acid catalysed removal of the tert-butyl group of tert-butyl esters of formula (I), wherein $R^1$, $R^2$, $R^3$, $R^4$, $L^1$ and $L^2$ are as hereinbefore defined, and Y is $-CO_2R^{15}$ (in which $R^{15}$ is $^tBu$), using standard reaction conditions.

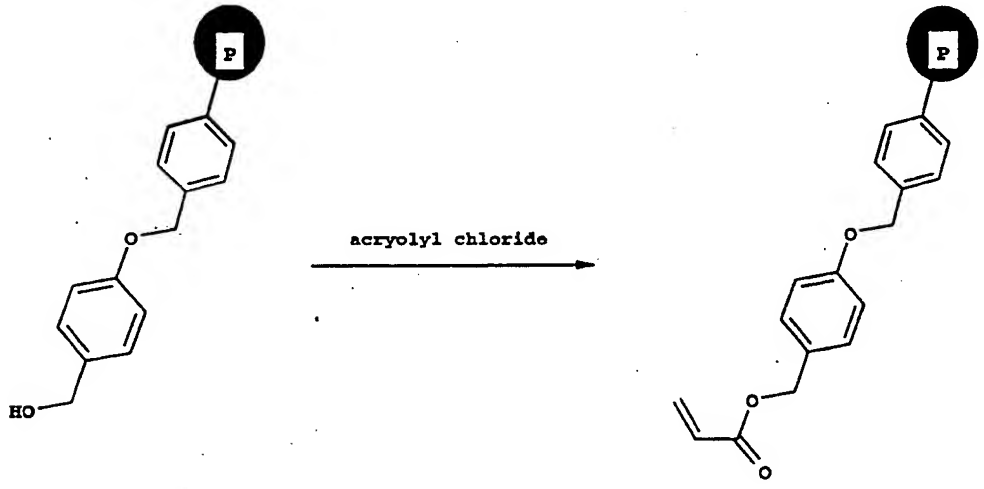
As another example compounds of formula (I) wherein $R^1$, $R^2$, $R^3$, $R^4$, $L^1$, $L^2$ and m are as hereinbefore defined and Y is carboxy may be prepared by hydrogenation of compounds of formula (I) wherein $R^1$, $R^2$, $R^3$, $R^4$, $L^1$, $L^2$ and m are as hereinbefore defined, and Y is $-CO_2R^{15}$ (in which $R^{15}$ is benzyl), in the presence of a suitable metal catalyst, e.g. platinum or palladium optionally supported on an inert carrier such as carbon, preferably in a solvent such

as methanol or ethanol. This reaction is most suitable for compounds of formula (I) where $R^3$ and $L^2$ do not contain carbon-carbon multiple bonds.

In a process A compounds of formula (I) wherein $R^2$, $R^3$, $R^4$, $L^1$, $L^2$ and m are as hereinbefore defined, Y is carboxy, and $R^1$ represents $R^{16}$-C(=O)- [where $R^{16}$ is $R^5$-, $R^5$-$L^4$-$R^7$- or $R^5$-$L^4$-$Ar^1$-$R^7$- and $R^5$, $R^7$, $L^4$ and $Ar^1$ are as hereinbefore defined] may be prepared by coupling of an acid with an amine to give an amide bond using standard peptide coupling procedures as described hereinafter.

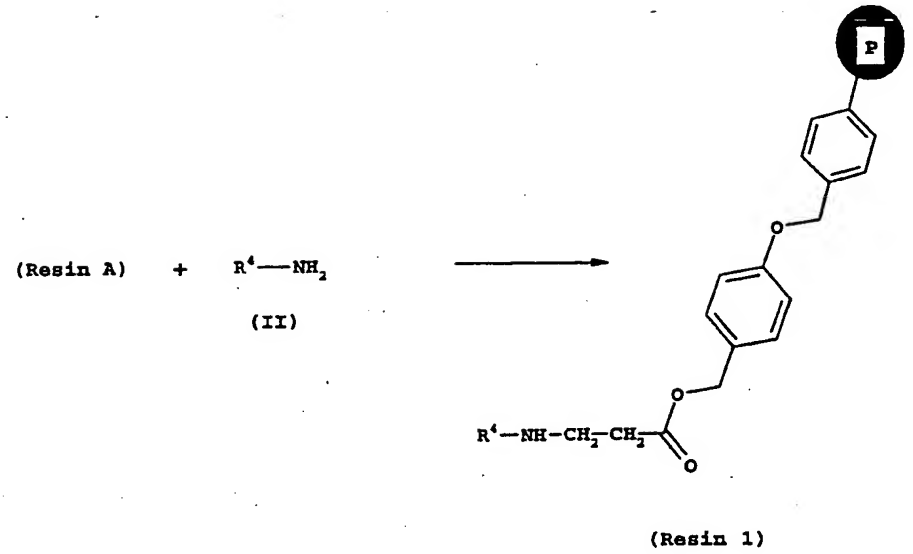
As an example of process A, compounds of formula (I) wherein $R^2$, $R^3$, $R^4$ and $L^1$ are as hereinbefore defined, Y is carboxy, $R^1$ represents $R^{16}$-C(=O)- , $L^2$ is an ethylene linkage and m is 1 may be prepared by:-

(i) treating Wang resin with acryloyl chloride, in the presence of a tertiary amine, such as diisopropylethylamine, in an inert solvent, such as dichloromethane, at a temperature at about room temperature, to give Resin A:

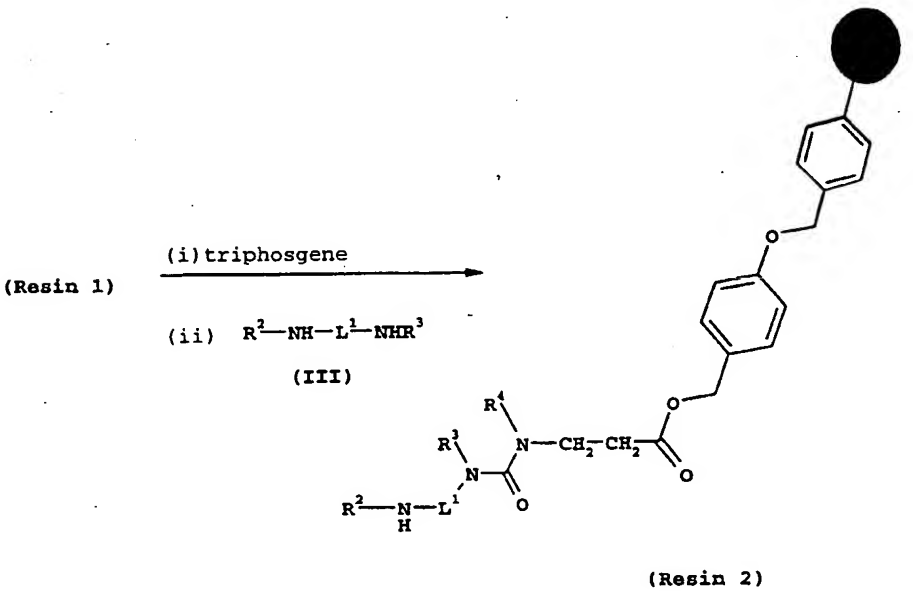



(Wang Resin) (Resin A)

(ii) reaction of Resin A with amines of formula (II) wherein $R^4$ is as defined hereinbefore, in the presence of a base, such as a tertiary organic base, for example diisopropylethylamine, in dimethylformamide and at a temperature at about room temperature to give Resin 1 in which $R^4$ is as defined hereinbefore:

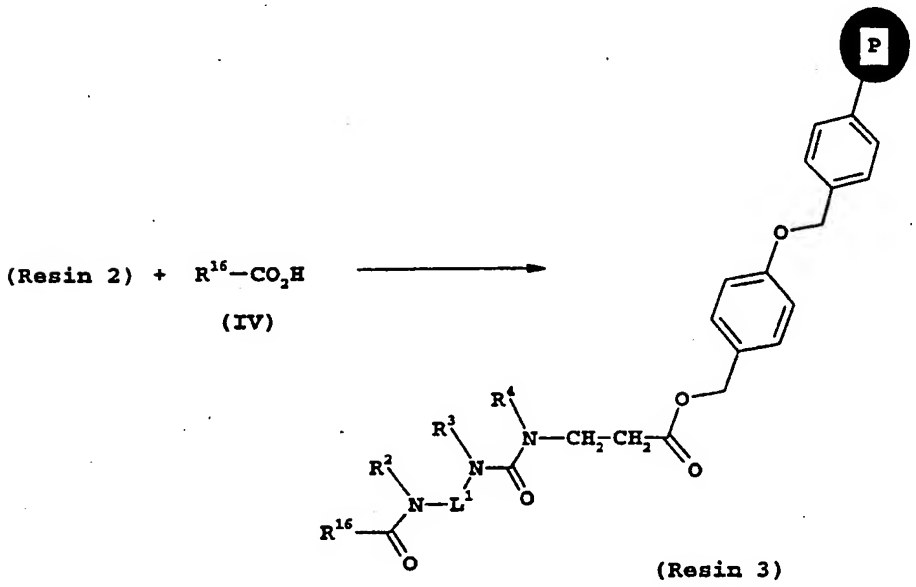



(iii) reaction of Resin 1 with triphosgene in the presence of diisopropylethylamine in dimethylformamide at a temperature at about room temperature followed by treatment with amines of formula (III) wherein $R^2$, $R^3$ and $L^1$ are as hereinbefore defined, in an inert solvent such as dichloromethane and at a temperature at about room temperature to give Resin 2 in which $R^2$, $R^3$,$R^4$ and $L^1$ are as defined hereinbefore.




(iv) reaction of Resin 2 with an acid of formula (IV) wherein $R^{16}$ is as hereinbefore defined, in the presence of O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium

hexafluorophosphate and diisopropylethylamine in dimethylformamide, at room temperature to give Resin 3 in which $R^2$, $R^3$,$R^4$ and $L^1$ are as defined hereinbefore.

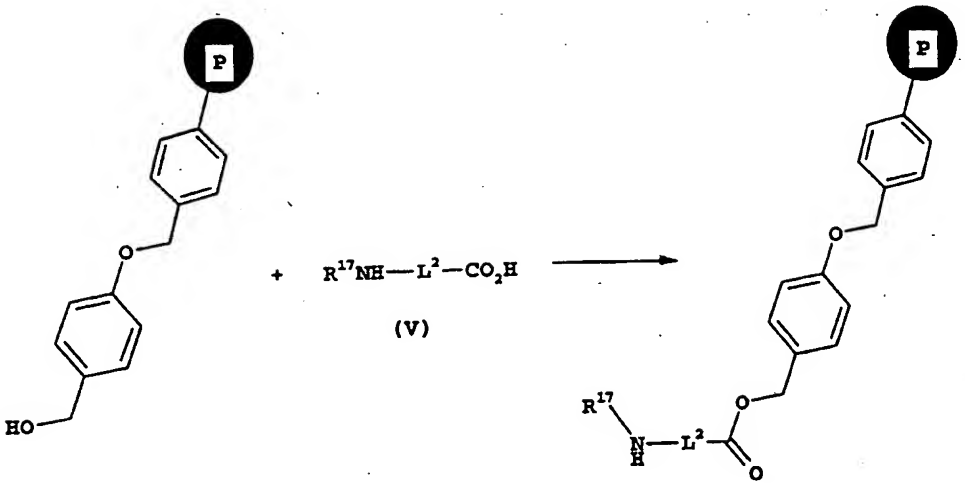



(v) treatment of Resin 3 with trifluoroacetic acid in an inert solvent such as dichloromethane and at a temperature at about room temperature.

This methodology is particularly suitable for the preparation of compounds of formula (I) in which $R^2$ and $R^3$ represent hydrogen, or $R^2$ and $R^3$ represent lower alkyl, or $R^2$ and $R^3$ together represent $-(CH_2)_n-$.

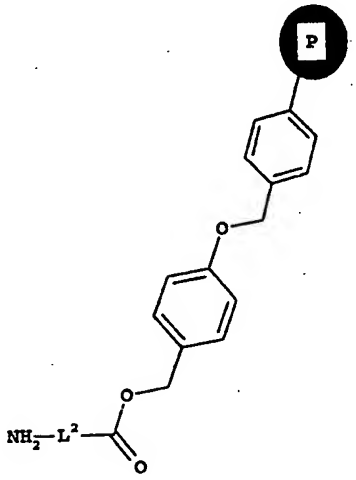
As another example of process A, compounds of formula (I) wherein $R^2$, $R^3$, $R^4$, $L^1$ and $L^2$ are as hereinbefore defined, Y is carboxy, $R^1$ represents $R^{16}$-C(=O)- and m is 1 may be prepared by:-

(i) treating Wang resin with a suitably protected amino-acid of formula (V)wherein $R^{17}$ is a suitable amino protecting group (such as 9-fluorenylmethoxycarbonyl) and n is as hereinbefore defined, in the presence of O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate and diisopropylethylamine in dimethylformamide, at room temperature to give Resin 4 wherein $R^{17}$ and $L^2$ are as hereinbefore defined:




(Wang Resin) (Resin 4)

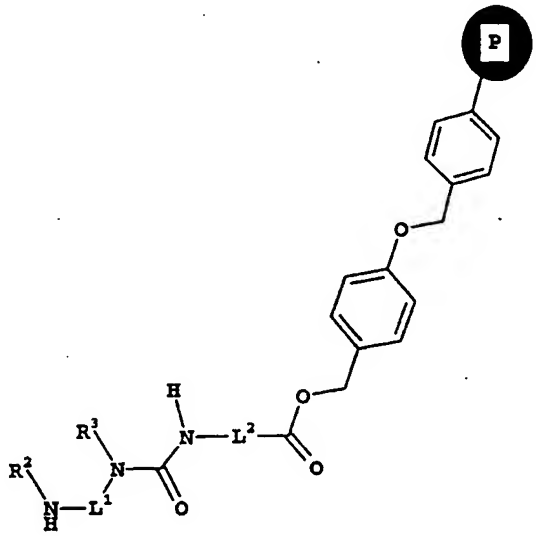
(ii) The resulting Resin 4, wherein $R^{17}$ and $L^2$ are as hereinbefore defined, may then be deprotected, for example by treating with piperidine in dimethylformamide, at room temperature, to give Resin 5 wherein $L^2$ is as hereinbefore defined:




(Resin 5)

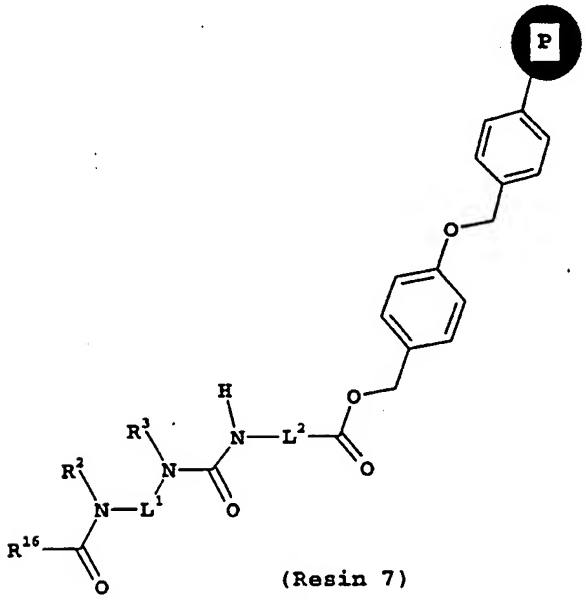
(iii) Resin 5 wherein $L^2$ is as hereinbefore defined, may then be treated with an alkyl or aryl-chloroformate, such as 4-nitrophenylchloroformate, in an inert solvent, such as tetrahydrofuran or dichloromethane, or a mixture of inert solvents, followed by reaction with an amine of formula (III) wherein $R^2$, $R^3$ and $L^1$ are as hereinbefore defined, in the presence of triethylamine, in an inert solvent such as

dimethylformamide and at a temperature at about room temperature to give resin 6 wherein $R^2$, $R^3$, $L^1$ and $L^2$ are as hereinbefore defined.



(Resin 6)

(iv) reaction of Resin 6 wherein $R^2$, $R^3$, $L^1$ and $L^2$ are as hereinbefore defined, with an acid of formula (IV) in which $R^2$, $R^3$,$R^4$ and $L^1$ are as defined hereinbefore, as described hereinabove, to give Resin 7.

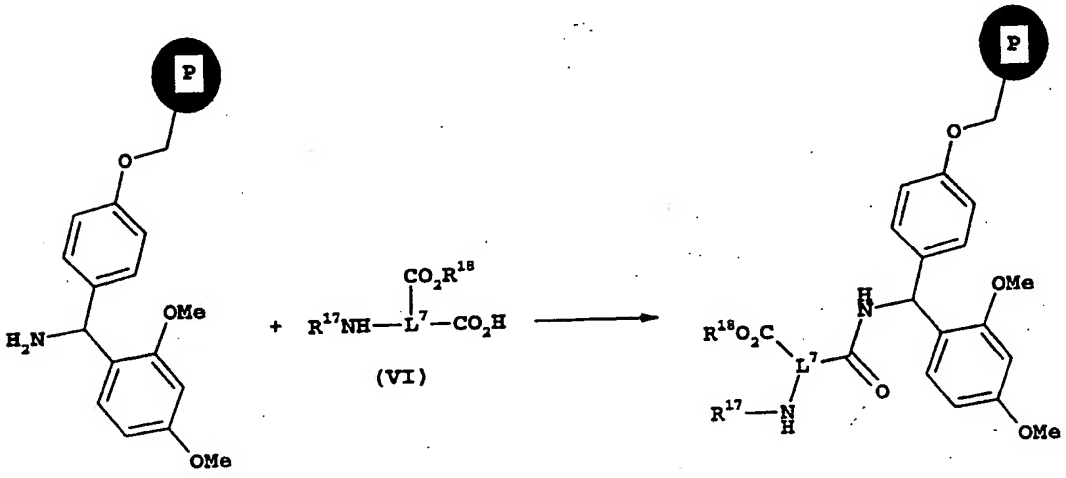


(Resin 7)

(v) treatment of Resin 7 with trifluoroacetic acid in an inert solvent such as dichloromethane and at a temperature at about room temperature.

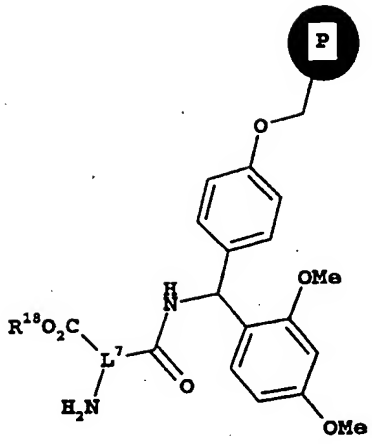
As another example of process A, compounds of formula (I) wherein $R^2$, $R^3$, $R^4$ and $L^1$ are as hereinbefore defined, Y is carboxy, $R^1$ represents $R^{16}$-C(=O)-, $L^2$ represents an alkylene linkage substituted by a $CONH_2$ group and m is 1 may be prepared by:-

(i) treating Rink Resin, with a suitably protected amino-acid of formula (VI) wherein $R^{17}$ is as hereinbefore defined, $R^{18}$ is a suitable carboxylic acid protecting group, such as tertiary butyl, and $L^7$ represents an alkylene linkage, to give resin 8 wherein $R^{17}$, $R^{18}$ and $L^7$ are as hereinbefore defined:



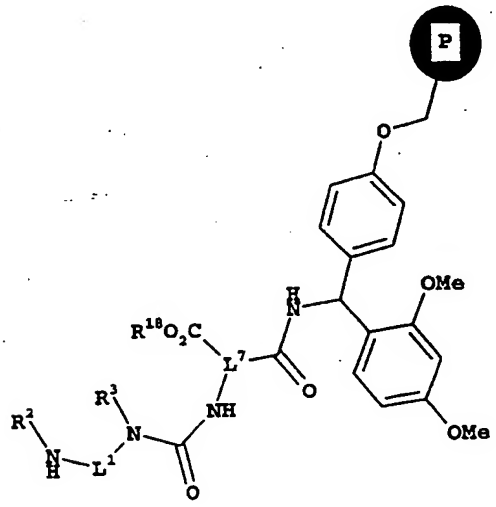

(Rink Resin) (Resin 8)

(ii) The resulting Resin 8 wherein $R^{17}$, $R^{18}$ and $L^7$ are as hereinbefore defined, may then be deprotected, for example by treating with piperidine in dimethylformamide, at room temperature, to give Resin 9 wherein $R^{18}$ and $L^7$ are as hereinbefore defined:



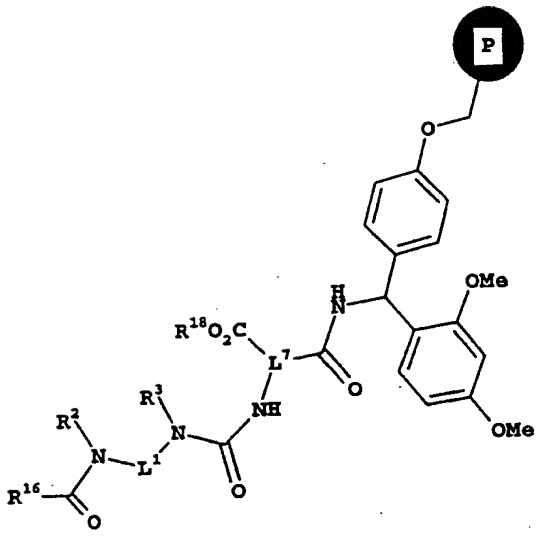

(Resin 9)

(iii) Resin 9 wherein $R^{18}$ and $L^7$ are as hereinbefore defined, may then be treated with an alkyl or aryl-chloroformate, followed by reaction with an amine of formula (III) wherein $R^2$, $R^3$ and $L^1$ are as hereinbefore defined, as described hereinabove, to give resin 10 wherein $R^2$, $R^3$, $R^{18}$, $L^1$ and $L^7$are as hereinbefore defined.




(Resin 10)

(iv) reaction of Resin 10 wherein $R^2$, $R^3$, $R^{18}$, $L^1$ and $L^7$are as hereinbefore defined, with an acid of formula (IV) in which $R^2$, $R^3$, $R^4$ and $L^1$ are as defined hereinbefore, as described hereinabove, to give Resin 11.

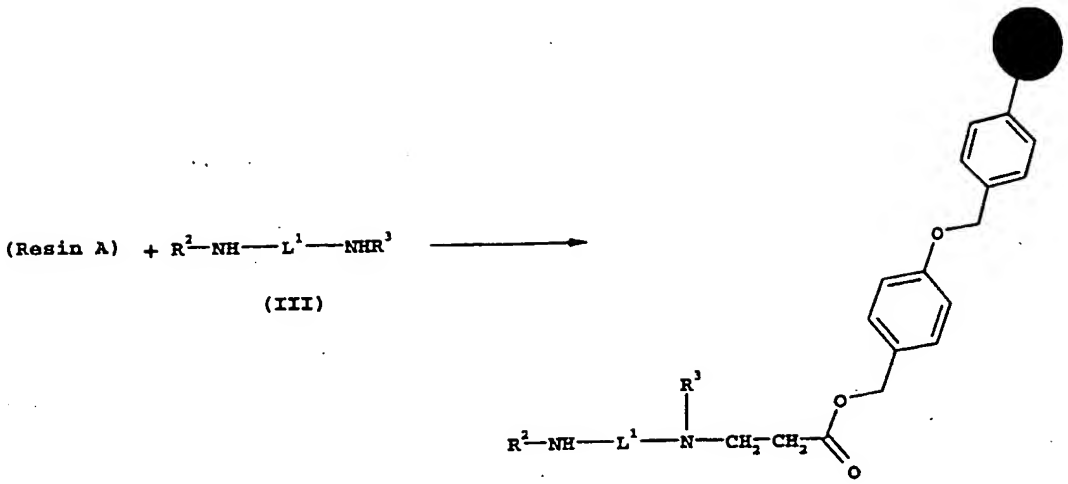


(Resin 11)

(v) treatment of Resin 11 with trifluoroacetic acid in an inert solvent such as dichloromethane and at a temperature at about room temperature.

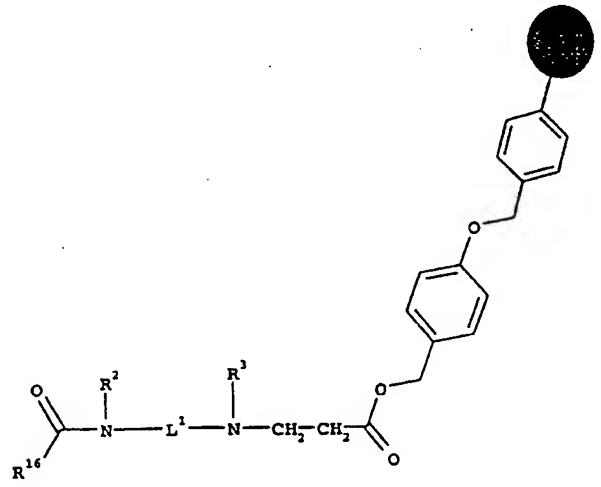
As another example of process A, compounds of formula (I) wherein $R^2$, $R^3$ and $L^1$ are as hereinbefore defined, Y is carboxy, $R^1$ represents $R^{16}$-C(=O)-, $L^2$ is an ethylene linkage and m is zero may be prepared by:-

(i) reaction of Resin A with diamines of formula (III) wherein $R^2$, $R^3$ and $L^1$ are as defined hereinbefore, in the presence of a base, such as a tertiary organic base, for example diisopropylethylamine, in dimethylformamide and at a temperature at about room temperature, to give Resin 12 in which $R^2$, $R^3$ and $L^1$ are as defined hereinbefore;




(Resin 12)

(ii) reaction of Resin 12 in which $R^2$, $R^3$ and $L^1$ are as defined hereinbefore with an acid of formula (IV), wherein $R^{16}$ is as hereinbefore defined, in the presence of O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate and diisopropylethylamine in dimethylformamide, to give Resin 13 in which $R^2$, $R^3$, $R^{16}$ and $L^1$ are as defined hereinbefore;

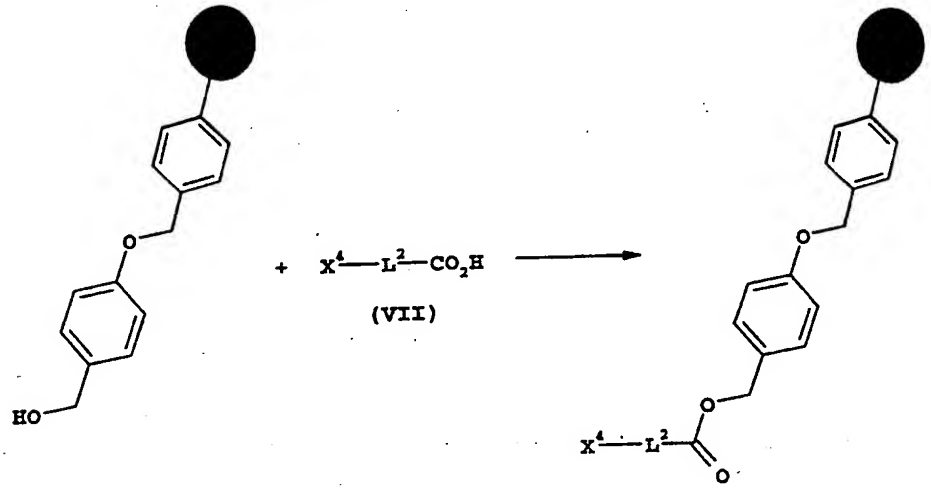



(Resin 13)

(iii) treatment of Resin 13 with trifluoroacetic acid in an inert solvent such as dichloromethane and at a temperature at about room temperature.

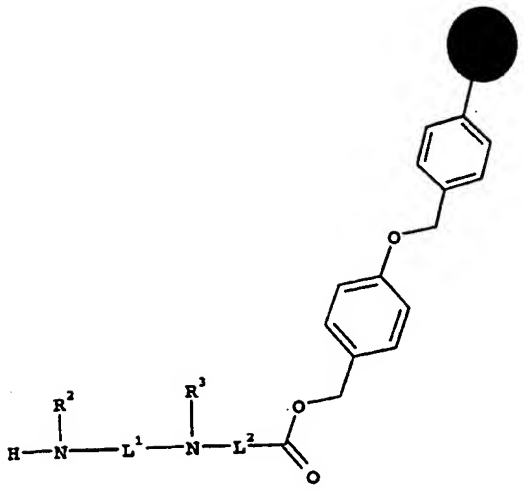
As another example of process A, compounds of formula (I), wherein $R^2$, $R^3$, $L^1$ and $L^2$ are as hereinbefore defined, Y is carboxy, $R^1$ represents $R^{16}$-C(=O)- and m is zero, may be prepared by:-

(i) treating Wang resin with a compound of formula (VII), wherein $L^2$ is as hereinbefore defined and $X^4$ is chloro, or preferably bromo, in the presence of a carbodiimide, such as didisopropylcarbodiimide, and 4-dimethylaminopyridine in a mixture of dimethylformamide and tetrahydrofuran, at room temperature, at room temperature to give Resin 3, wherein $L^2$ and $X^4$ are as hereinbefore defined;



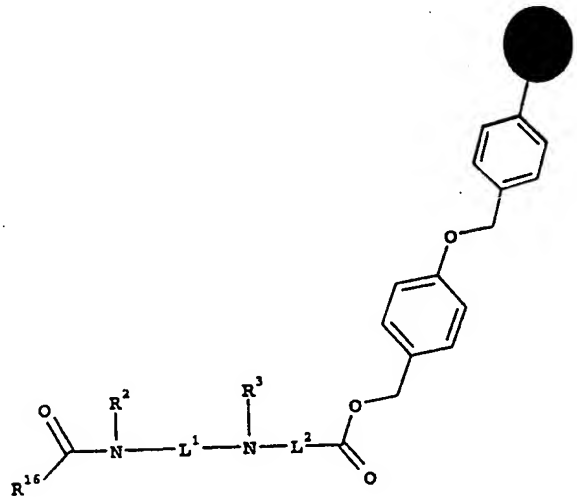

(Wang Resin) (Resin 14)

(ii) reaction of Resin 14 wherein $L^2$ and $X^4$ are as hereinbefore defined, with diamines of formula (III) wherein $R^2$, $R^3$ and $L^1$ are as hereinbefore defined in an inert solvent, such as dimethylformamide, at a temperature at about room temperature, to give Resin 15 wherein $R^2$, $R^3$, $L^1$,and $L^2$ are as hereinbefore defined;



(Resin 15)

(iii) reaction of Resin 15 wherein $R^2$, $R^3$, $L^1$ and $L^2$ are as hereinbefore defined, with acids of formula (IV), wherein $R^{16}$ is as hereinbefore defined, using standard peptide coupling conditions as described hereinabove, to give Resin 16 wherein $R^2$, $R^3$, $R^{16}$, $L^1$ and $L^2$ are as hereinbefore defined;

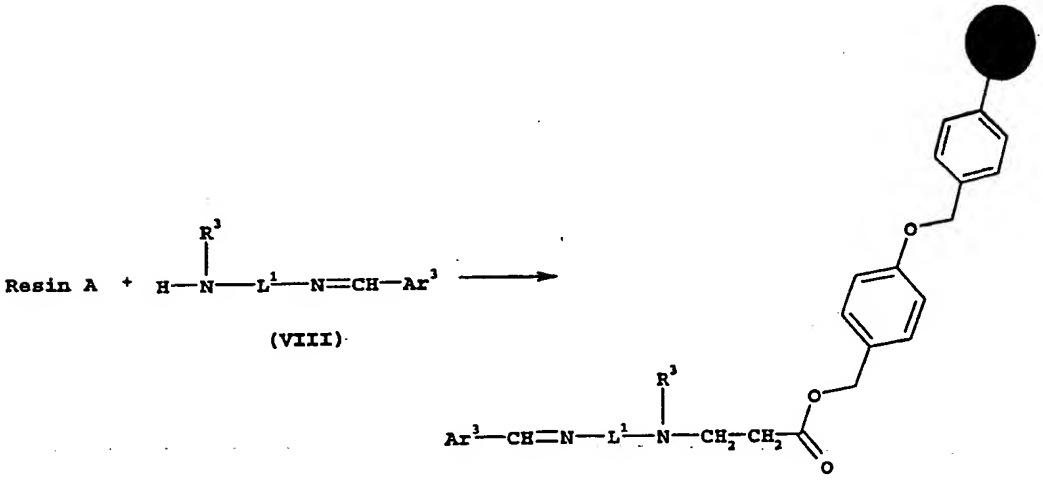


(Resin 16)

(iv) treatment of Resin 16 with trifluoroacetic acid in an inert solvent such as dichloromethane and at a temperature at about room temperature.

As another example of process A, compounds of formula (I), wherein $R^3$ and $L^1$ are as hereinbefore defined, $R^2$ is hydrogen, $L^2$ is an ethylene linkage, Y is carboxy, $R^1$ represents $R^{15}$-C(=O)- (in which $R^{15}$ is as hereinbefore defined) and m is zero, may be prepared by:-

(i) reaction of Resin A with amines of formula (VIII) wherein $R^3$ and $L^1$ are as defined hereinbefore, and $Ar^3$ is 3,4-dimethoxyphenyl, in the presence of a base, such as a tertiary organic base, for example diisopropylethylamine, in an inert solvent, such as dimethylsulphoxide and at a temperature at about room temperature, to give Resin 17 in which $R^3$, $L^1$ and $Ar^3$ are as defined hereinbefore;




(Resin 17)

(ii) reaction of Resin 17 wherein $R^3$, $L^1$ and $Ar^3$ are as defined hereinbefore, with trifluoroacetic acid, in a mixture of acetonitrile and water, and at a temperature at about room temperature, to give Resin 12 wherein $R^3$ and $L^1$ are as defined hereinbefore and $R^2$ is hydrogen;

(iii) reaction of Resin 12 wherein $R^3$ and $L^1$ are as defined hereinbefore and $R^2$ is hydrogen, with acids of formula (IV), wherein $R^{16}$ is as hereinbefore defined, using standard peptide coupling conditions as described hereinabove, to give resin 13 wherein $R^3$, $L^1$ and $R^{16}$ are as defined hereinbefore and $R^2$ is hydrogen;

(iv) reaction of Resin 13 wherein $R^3$, $L^1$ and $R^{16}$ are as defined hereinbefore and $R^2$ is hydrogen, with trifluoroacetic acid as described hereinabove.

According to a further process B compounds of the invention may be prepared by interconversion of other compounds of the invention.

For example compounds of formula (I), wherein $R^1$, $R^2$, $R^3$, $R^4$, $L^1$, $L^2$ and m are as hereinbefore defined and Y is a group -C(=O)-NHOH may be prepared by reaction of compounds of formula (I), wherein $R^1$, $R^2$, $R^3$, $R^4$, $L^1$, $L^2$ and m are as hereinbefore defined and Y is carboxy, with hydroxylamine using standard peptide coupling procedures such as treatment with a carbodiimide, for example dicyclohexylcarbodiimide, in the presence of triethylamine, in an inert solvent such as dichloromethane or tetrahydrofuran and at a temperature at about room temperature. The coupling may also be carried out using 1-hydroxybenzotriazole and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide in dichloromethane at room temperature. The preparation may also be carried out using an O-protected hydroxylamine such as O-(trimethylsilyl)hydroxylamine, O-(t-butyldimethylsilyl)-hydroxylamine, or O-(tetrahydropyranyl)hydroxylamine followed by treatment with acid.

As another example of the interconversion process, compounds of formula (I) containing sulphoxide linkages may be prepared by the oxidation of corresponding compounds containing -S- linkages. For example, the oxidation may conveniently be carried out by means of reaction with a peroxyacid, e.g. 3-chloroperbenzoic acid, preferably in an inert solvent, e.g. dichloromethane, preferably at or near room temperature, or alternatively by means of potassium hydrogen peroxomonosulphate in a medium such as aqueous methanol, buffered to about pH5, at temperatures between about 0°C and room temperature. This latter method is preferred for compounds containing an acid-labile group.

As another example of the interconversion process, compounds of formula (I) containing sulphone linkages may be prepared by the oxidation of corresponding compounds containing -S- or sulphoxide linkages. For example, the oxidation may conveniently be carried out by means of reaction with a peroxyacid, e.g. 3-chloroperbenzoic acid, preferably in an inert solvent, e.g. dichloromethane, preferably at or near room temperature.

It will be appreciated that compounds of the present invention may contain asymmetric centres. These asymmetric centres may independently be in either the R or S configuration. It will be apparent to those skilled in the art that certain compounds of the invention may also exhibit geometrical isomerism. It is to be understood that the present invention includes individual geometrical isomers and stereoisomers and mixtures thereof, including racemic mixtures, of compounds of formula (I) hereinabove. Such isomers can be separated from their mixtures, by the application or adaptation of known methods, for example chromatographic techniques and recrystallisation techniques, or they are separately prepared from the appropriate isomers of their intermediates.

According to a further feature of the invention, acid addition salts of the compounds of this invention may be prepared by reaction of the free base with the appropriate acid, by the application or adaptation of known methods. For example, the acid addition salts of the compounds of this invention may be prepared either by dissolving the free base in water or aqueous alcohol solution or other suitable solvents containing the appropriate acid and isolating the salt by evaporating the solution, or by reacting the free base and acid in an organic solvent, in which case the salt separates directly or can be obtained by concentration of the solution.

The acid addition salts of the compounds of this invention can be regenerated from the salts by the application or adaptation of known methods. For example, parent compounds of the invention can be regenerated from their acid addition salts by treatment with an alkali, e.g. aqueous sodium bicarbonate solution or aqueous ammonia solution.

Compounds of this invention can be regenerated from their base addition salts by the application or adaptation of known methods. For example, parent compounds of the invention can be regenerated from their base addition salts by treatment with an acid, e.g. hydrochloric acid.

Compounds of the present invention may be conveniently prepared, or formed during the process of the invention, as solvates (e.g. hydrates). Hydrates of compounds of the present invention may be conveniently prepared by recrystallisation from an aqueous/organic solvent mixture, using organic solvents such as dioxan, tetrahydrofuran or methanol.

According to a further feature of the invention, base addition salts of the compounds of this invention may be prepared by reaction of the free acid with the appropriate base, by the application or adaptation of known methods. For example, the base addition salts of the compounds of this invention may be prepared either by dissolving the free acid in water or

aqueous alcohol solution or other suitable solvents containing the appropriate base and isolating the salt by evaporating the solution, or by reacting the free acid and base in an organic solvent, in which case the salt separates directly or can be obtained by concentration of the solution.

The starting materials and intermediates may be prepared by the application or adaptation of known methods, for example methods as described in the Reference Examples or their obvious chemical equivalents.

Esters of formula (I), wherein $R^1$, $R^2$, $R^3$, $R^4$, $L^1$ and $L^2$ are as hereinbefore defined, Y is a $-CO_2R^{15}$ group (in which $R^{15}$ is as hereinbefore defined) and m is 1 may be prepared by standard reactions, such as acylation, alkylation or sulphonylation, from compounds of formula (1):-

$$HN(R^2)\text{-}L^1\text{-}N(R^3)\text{-}C(=O)\text{-}N(R^4)\text{-}L^2\text{-}CO_2R^{15} \qquad (1)$$

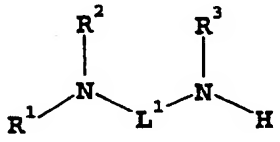
wherein $R^2$, $R^3$, $R^4$, $R^{15}$, $L^1$ and $L^2$ are as hereinbefore defined. For example esters of formula (I) where $R^1$ represents $R^5\text{-}L^3\text{-}$ (in which $R^5$ is as hereinbefore defined and $L^3$ is a $-C(=O)-$ linkage) may be prepared using $R^5\text{-}C(=O)\text{-}Cl$ (in which $R^5$ is as hereinbefore defined) as the acylating agent. As another example esters of formula (I) where $R^1$ represents $R^5\text{-}L^3\text{-}$ (in which $R^5$ is as hereinbefore defined and $L^3$ is a direct bond) may be prepared using $R^5\text{-}X^4$ (in which $R^5$ is as hereinbefore defined and $X^4$ is a halogen atom) as the alkylating agent. As another example esters of formula (I) where $R^1$ represents $R^5\text{-}L^3\text{-}$ (in which $R^5$ is as hereinbefore defined and $L^3$ is a $-SO_2-$ linkage) may be prepared using $R^5\text{-}SO_2Cl$ (in which $R^5$ is as hereinbefore defined) as the sulphonylating agent.

Compounds of formula (1), wherein $R^2$, $R^3$, $R^4$, $R^{15}$, $L^1$ and $L^2$ are as hereinbefore defined, may be prepared by reaction of compounds of formula (2):-

$$HN(R^4)\text{-}L^2\text{-}CO_2R^{15} \qquad (2)$$

wherein $R^4$, $R^{15}$ and $L^2$ are as hereinbefore defined, with amines of formula (III), wherein $R^2$, $R^3$ and $L^1$ are as hereinbefore defined, in the presence of triphosgene as described hereinbefore.

Esters of formula (I), wherein $R^1$, $R^2$, $R^3$, $L^1$ and $L^2$ are as hereinbefore defined, Y is a $-CO_2R^{15}$ group (in which $R^{15}$ is as hereinbefore defined ) and m is zero, may be prepared by reaction of compounds of formula (3):-



(3)

wherein $R^1$, $R^2$, $R^3$ and $L^1$ are as hereinbefore defined with compounds of formula (4):-

$$X^5\text{-}L^2\text{-}CO_2R^{15} \qquad (4)$$

wherein $R^{15}$ and $L^2$ are as hereinbefore defined and $X^5$ is a leaving group such as an alkyl or aryl sulphonate (for example methanesulphonate or 4-methylphenylsulphonate), or a halogen atom.

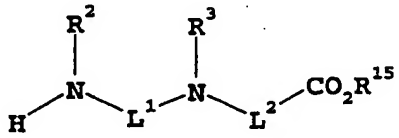
Compounds of formula (3), wherein $R^1$, $R^2$, $R^3$ and $L^1$ are as hereinbefore defined, may be prepared by standard reactions, such as acylation, peptide coupling, reductive amination, alkylation and sulphonylation, from diamines of formula (III), wherein $R^2$, $R^3$ and $L^1$ are as defined hereinbefore. For example compounds of formula (3) where $R^1$ represents $R^{16}$ -C(=O)- may be prepared using compounds of formula (5):-

$$R^{16}\text{-}C(=O)\text{-}X^6 \qquad (5)$$

wherein $R^{16}$ is as hereinbefore defined and $X^6$ is bromo or chloro, as the acylating agent. Compounds of formula (1) where $R^1$ represents $R^{16}$ -C(=O)- may be also be prepared by peptide coupling of diamines of formula (III) with compounds of formula (5) where $X^6$ is hydroxy. As another example compounds of formula (3), where $R^1$ represents $R^5\text{-}L^4\text{-}Ar^1\text{-}L^6\text{-}R^6$- (in which $R^5$, $L^6$, $L^4$ and $Ar^1$ are as hereinbefore defined and $R^6$ is for example methylene), may be prepared by a reductive amination reaction of the diamine (III) with the aldehyde $R^5\text{-}L^4\text{-}Ar^1\text{-}L^6\text{-}CHO$. As another example compounds of formula (3), where $R^1$ contains a $-R^6$-

linkage, may be prepared using $R^1$-$X^4$ (in which $R^1$ contains a -$R^6$- linkage and $X^4$ is a halogen atom) as the alkylating agent. As another example compounds of formula (3), where $R^1$ represents $R^5$-$L^3$-, $R^5$-$L^4$-$R^7$-$L^5$-, $R^5$-$L^4$-$Ar^1$-$L^3$- or $R^5$-$L^4$-$Ar^1$-$R^7$-$L^5$- (in which $R^5$, $R^7$, $L^4$ and $Ar^1$ are as hereinbefore defined and $L^3$ or $L^5$ is a -$SO_2$- linkage), may be prepared using $R^5$-$SO_2Cl$, $R^5$-$L^4$-$R^7$-$SO_2Cl$, $R^5$-$L^4$-$Ar^1$-$SO_2Cl$ or $R^5$-$L^4$-$Ar^1$-$R^7$-$SO_2Cl$ respectively as the sulphonylating agent.

Esters of formula (I), wherein $R^1$, $R^2$, $R^3$, $R^4$, $L^1$ and $L^2$ are as hereinbefore defined, Y is a -$CO_2R^{15}$ group and m is zero, may also be prepared by standard acylation, peptide coupling, reductive amination, alkylation and sulphonylation reactions, from compounds of formula (6):-



(6)

wherein $R^2$, $R^3$, $R^{15}$, $L^1$ and $L^2$ are as hereinbefore defined. For example esters of formula (I) where $R^1$ represents $R^{16}$-C(=O)- may be prepared using compounds of formula (5) wherein $R^{16}$ is as hereinbefore defined and $X^6$ is bromo or chloro, as the acylating agent. As another example esters of formula (I) where $R^1$ represents $R^{16}$-C(=O)- may be also be prepared by peptide coupling using compounds of formula (5) where $X^6$ is hydroxy. As another example esters of formula (I) where $R^1$ contains a -$R^6$- linkage, may be prepared using $R^1$-$X^4$ (in which $R^1$ contains a -$R^6$- linkage and $X^4$ is a halogen atom) as the alkylating agent. As another example esters of formula (I), where $R^1$ represents $R^5$-$L^3$-, $R^5$-$L^4$-$R^7$-$L^5$-, $R^5$-$L^4$-$Ar^1$-$L^3$- or $R^5$-$L^4$-$Ar^1$-$R^7$-$L^5$- (in which $R^5$, $R^7$, $L^4$ and $Ar^1$ are as hereinbefore defined and $L^3$ or $L^5$ is a -$SO_2$- linkage), may be prepared using $R^5$-$SO_2Cl$, $R^5$-$L^4$-$R^7$-$SO_2Cl$, $R^5$-$L^4$-$Ar^1$-$SO_2Cl$ or $R^5$-$L^4$-$Ar^1$-$R^7$-$SO_2Cl$ respectively as the sulphonylating agent.

Compounds of formula (6) wherein $R^2$, $R^3$, $R^{15}$, $L^1$ and $L^2$ are as hereinbefore defined, may be prepared by reaction of diamines of formula (III), wherein $R^2$, $R^3$ and $L^1$ are as hereinbefore defined, with compounds of formula (4), wherein $R^{15}$, $L^2$ and $X^5$ are as hereinbefore defined.

Intermediates of formulae (1), (6), (Resin 1), (Resin 2), (Resin 3), (Resin 4), (Resin 5), (Resin 6), (Resin 7), (Resin 8), (Resin 9), (Resin 10), (Resin 11), (Resin 12), (Resin 13), (Resin 14), (Resin 15), (Resin 16) and (Resin 17) are novel compounds and, as such, they and their processes described herein for their preparation constitute further features of the present invention.

The present invention is further Exemplified but not limited by the following illustrative Examples and Reference Examples.

Mass spectra were recorded using total loop electrospray technique[MS(ES)].

Mass spectra [MS(ES)] for compounds A to DB were determined using a Micromass Platform II mass spectrometer fitted with an Electrospray source and an HP1100 liquid chromatograph (5 micron Hypersil Elite C18 HPLC column operated under gradient elution conditions with a mixture of acetonitrile and water plus 0.1% trifluoroacetic acid as the mobile phase [0-3 minutes 20% acetonitrile; 3-15 minutes ramp up to 80% acetonitrile; 15 minutes to end of run 80% acetonitrile, flow rate 0.3ml/minute and using evaporative light scattering (ELS) for detection].

Mass spectra [MS(ES)] for Compounds KT to LQ were determined using a Finnigan TSQ700 mass spectrometer, Hypersil Elite C18 5micron column (4.6mm i.d. x 150mm) operated under gradient elution conditions (0-2 minutes 95:5, A:B then 2-12min 95:5 to 5:95% A:B, solvent A is a mixture of water 0.1%trifluoroacetic acid and solvent B is a mixture of acetonitrile and 0.1%trifluoroacetic acid ) and using UV detection at 220nm.

Mass spectra [MS(ES)] for Compounds DC to EZ, FA to JH, LG and MH to NJ were determined using inline ELS and Diode Array detection, a Phenomenex Luna 3μ C18 (2) 30x4.6mm column and gradient elution with a flow rate of 2ml/minute and mixtures of (A) 0.1% trifluoroacetic acid in water and (B) 0.1% trifluoroacetic acid in acetonitrile, v/v (0 minutes, 95:5, A:B; 0.5 minutes, 95;5, A:B; 4.5 minutes, 5:95, A:B; 5.0 minutes, 95:5, A:B; 5.5 minutes, 95:5).

Mass spectra [MS(ES)] for Compounds LJ, LK and LL were determined using by ESI-LC-MS using gradient elution conditions: 0.00 minutes, 9:1, A:B; 9.50 minutes 5:95. A:B; 14.5 minutes 5:95, A:B; 19.5 minutes 9:1, A:B; 21.5 minutes 9:1, A:B (where A is 0.01% ammonium acetate and water and B is 0.01% ammonium acetate and methanol).

High Pressure Liquid Chromatography (HPLC) conditions for determination of retention times ($R_T$) using an Elite C-18, 5micron column (4.6mm i.d. x 150mm) and ELS detector were:- (i) for compounds A to DB, solvent acetonitrile/water gradient (both buffered with 0.5 % trifluoroacetic acid): 20% acetonitrile for 3 minutes; than ramp up to 80% over the next 12 minutes; maintain at 80% acetonitrile for 3 minutes; then ramp back to 20% acetonitrile over

0.5 minutes (total run time 20 minutes); (ii) for compounds KT to LQ, Method A: 0-2 minutes 90:10, A:B then 2-22mins 90:10 to 90:10, A:B, Method B: 0-1 minutes 90:10, A:B then 1-13mins 90:10 to 90:10, A:B, Method C: 0-2 minutes 70:30, A:B then 2-12minutes 70:30 to 40:60, A:B (where solvent A=water and 0.05% trifluoroacetic acid ; solvent B=Acetonitrile and 0.05% trifluoroacetic acid).

Preparative HPLC conditions for compounds KT, KW, LA, LD and LF were:- Hypersil Elite C18 5micron column (25mm i.d. x 100mm) operated under gradient elution conditions Method D: 0-3 minutes 70:30, A:B then 3-26minutes 70:30 to 30:70, A:B (where solvent A=water and 0.05% trifluoroacetic acid ; solvent B=Acetonitrile and 0.05% trifluoroacetic acid).

## EXAMPLE 1

Compounds A, B to BI and LM to LQ.

Step 1. A suspension of Wang resin (15g , Advanced ChemTech) in dichloromethane (200ml) was treated with diisopropylethylamine (9ml) then with acryloyl chloride (4.5ml). The mixture was kept at ambient temperature for 3 hours with occasional agitation. The resin was filtered and then washed three times with 50ml portions each of dichloromethane, tetrahydrofuran, dimethylformamide, tetrahydrofuran and dichloromethane, and then dried under vacuum.

Step 2. The acrylate-loaded Wang resin from Step 1 (1.0g, 0.83mmol/g loading) was swelled with dimethylformamide (15ml) and then treated with 1-(3-aminopropyl)-2-pyrrolidinone (1.2ml). The mixture was shaken gently for 18 hours. The resin was drained and then washed three times with dimethylformamide, three times with tetrahydrofuran three times with dichloromethane then sucked dry.

Step 3. The resin from Step 2 was swelled in dichloromethane (20ml), then treated with diisopropylethylamine (1.44ml) and treated with triphosgene (0.74g). There was a slight exotherm and some evolution of gas. The mixture was gently agitated for 2 hours, then washed four times with dichloromethane and then sucked dry. A solution of homopiperazine (0.83g) and pyridine (0.67ml) in dichloromethane (15ml) was added to the resin and the mixture was gently agitated for 2 hours. The resin was then drained, washed thoroughly with five portions of dichloromethane and then dried under vacuum.

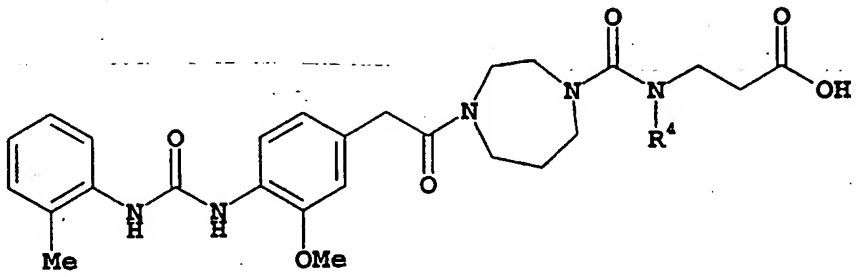
Step 4. The resin from Step 3 was treated with a solution of 3-methoxy-4-[3-(2-methylphenyl)ureido]phenylacetic acid (0.52g, prepared as described in Example 52B of International Patent Application Publication No. WO 96/22966), O-(7-azabenzotriazol-1-yl)-

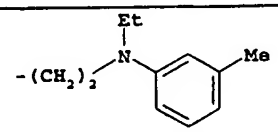
1,1,3,3-tetramethyluronium hexafluorophosphate (0.63g) and diisopropylethylamine (0.87ml) in dimethylformamide (20ml). After standing at room temperature for 18 hours the mixture was drained and the resin was washed three times with dimethylformamide, then three times with tetrahydrofuran, then three times with dichloromethane and then dried under vacuum.

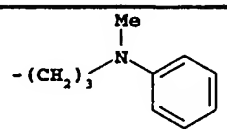
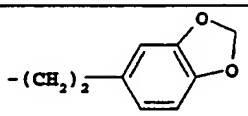
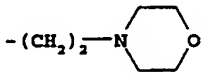
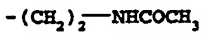
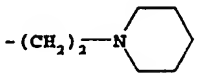
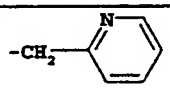
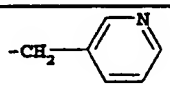
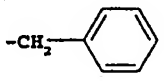
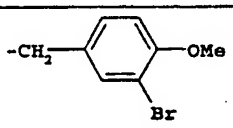
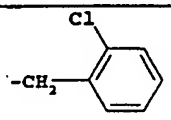
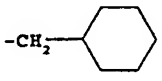
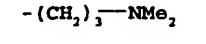
Step 5. The resin from Step 4 was treated with a mixture of trifluoroacetic acid and dichloromethane (15ml , 1:1, v/v). After 1 hour, the resin was drained and then washed twice with a mixture of trifluoracetic acid and dichloromethane (5ml, 1:1, v/v). The combined filtrate and washings was evaporated to dryness. The residue was triturated with diethyl ether to give 3-{[(4-{[3-methoxy-4-(2-methylphenylureido)-phenyl]-acetyl}-homopiperazin-1-yl)-carbonyl]-[3-(2-oxo-pyrrolidin-1-yl)-propyl]-amino}-propionic acid (0.39g, Compound A) as a yellow amorphous solid. MS: $(M-H)^-$ 635. HPLC: $R_T$=11.45 minutes (gradient elution using a mixture of acetonitrile and water, 1:4 to 4:1, v/v).

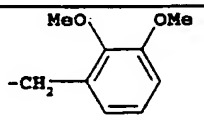
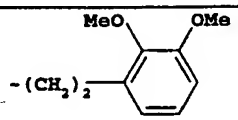
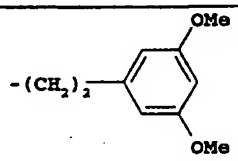
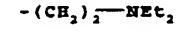
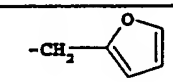
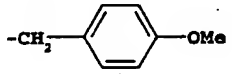
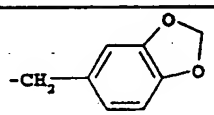
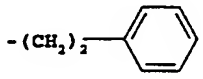
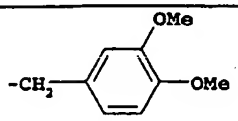
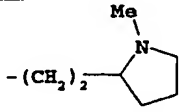
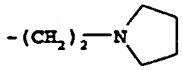
By proceeding in a similar manner to Example 1, but using the appropriately substituted amines in step 2, there were prepared Compounds B to AG depicted in Table 1.

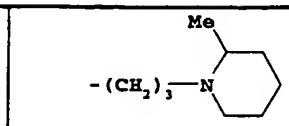
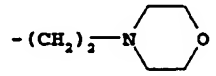
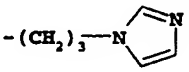
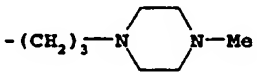
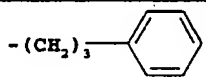
TABLE 1




| Compound number | $R^4$ | MOLECULAR FORMULA | HPLC $R_T$ (minutes) | MS(ES) $MH^+$ | MS(ES) $MH^-$ |
|---|---|---|---|---|---|
| Compound B |  | C37H48N6O6 | 13 | 673 | 671 |

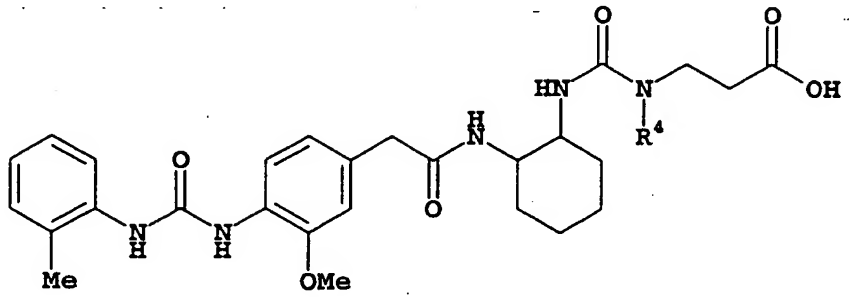
| | | | | | |
|---|---|---|---|---|---|
| Compound C |  | C36H46N6O6 | 12 | 659 | 657 |
| Compound D |  | C35H41N5O8 | 10.5 | | |
| Compound F |  | C32H44N6O7 | 10.9 | 625 | 624 |
| Compound G |  | C30H40N6O7 | 10.8 | 597 | 595 |
| Compound H |  | C33H46N6O6 | 11.5 | 623 | 621 |
| Compound I |  | C32H38N6O6 | 12 | 629 | 627 |
| Compound J |  | C32H38N6O6 | 10.6 | 603 | 601 |
| Compound K |  | C33H39N5O6 | 13.9 | 602 | 600 |
| Compound L |  | C34H40BrN5O7 | 14.9 | 724/726 | 725/722 |
| Compound M |  | C33H38ClN5O6 | 14.4 | 636 | 634 |
| Compound N |  | C33H45N5O6 | 15 | 608 | 607 |
| Compound O |  | C31H44N6O6 | 10.5 | 597 | |
| Compound P |  | C30H42N6O6 | 10.6 | | 581 |

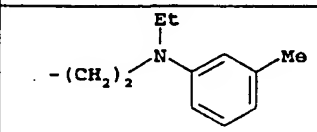
| | | | | | |
|---|---|---|---|---|---|
| Compound Q |  | C31H43N5O6 | 13.9 | 582 | 580 |
| Compound R |  | C35H43N5O8 | 10.7 | 662 | 660 |
| Compound S |  | C36H45N5O8 | 15 | 676 | 674 |
| Compound T |  | C36H45N5O8 | 14.3 | 676 | |
| Compound U |  | C32H46N6O6 | 11.3 | 611 | |
| Compound V |  | C31H37N5O7 | 11 | | 624 |
| Compound W |  | C34H41N5O7 | 11 | | |
| Compound X |  | C34H39N5O8 | 11 | | |
| Compound Y |  | C34H41N5O6 | 14.3 | 616 | 614 |
| Compound Z |  | C35H43N5O8 | 11 | | 660 |
| Compound AA |  | C33H46N6O6 | 10.7 | 623 | |
| Compound AB |  | C32H44N6O6 | 11 | 609 | 608 |

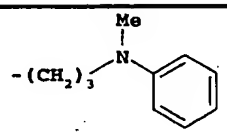
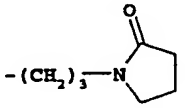
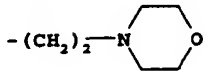
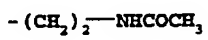
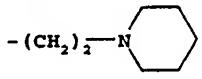
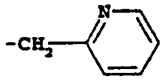
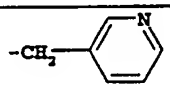
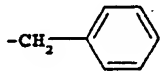
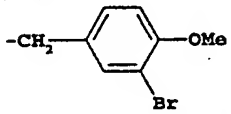
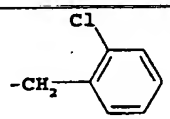
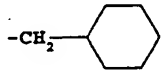
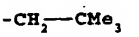
| | | | | | |
|---|---|---|---|---|---|
| Compound AC |  | C35H50N6O6 | 11.5 | 651 | |
| Compound AD |  | C33H46N6O7 | 10.6 | 639 | |
| Compound AE |  | C32H41N7O6 | 10.2 | 620 | 618 |
| Compound AF |  | C34H49N7O6 | 9.4 | 652 | |
| Compound AG |  | C35H43N5O6 | 14.9 | 630 | 629 |

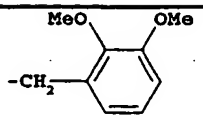
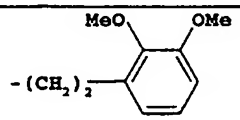
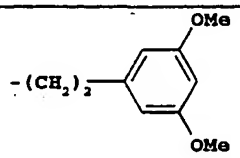
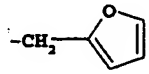
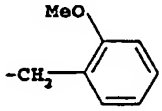
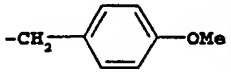
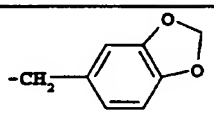
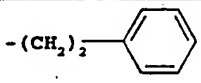
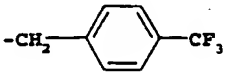
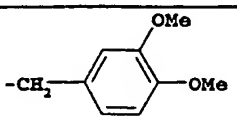
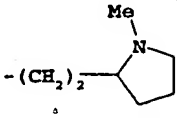
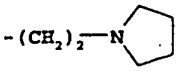
By proceeding in a similar manner to Example 1, but using the appropriately substituted amines in step 2, and 1,2-diaminocyclohexane in step 3 there were prepared Compounds AH to BI depicted in Table 2.

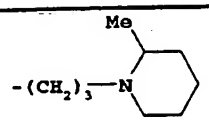
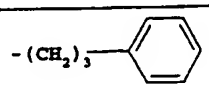
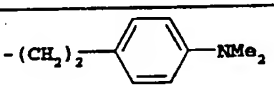
TABLE 2



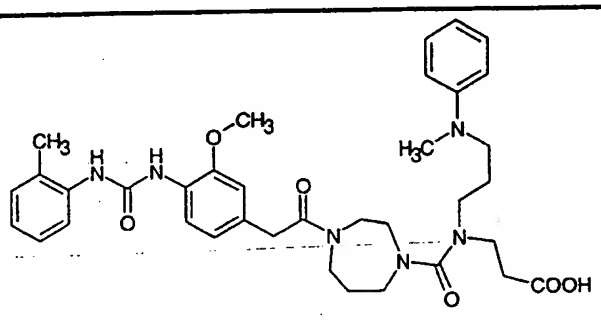
| Compound number | $R^4$ | MOLECULAR FORMULA | HPLC $R_T$ (minutes) | MS(ES) $MH^+$ | MS(ES) $MH^-$ |
|---|---|---|---|---|---|
| Compound AH |  | C38H50N6O6 | 14.2 | 687 | 685 |

| | | | | | |
|---|---|---|---|---|---|
| Compound AI |  | C37H48N6O6 | 13 | 673 | 671 |
| Compound AJ |  | C34H46N6O7 | 12.2 | 651 | 649 |
| Compound AK |  | C33H46N6O7 | 12.2 | 639 | 637 |
| Compound AL |  | C31H42N6O7 | 11.8 | 611 | 609 |
| Compound AM |  | C34H48N6O6 | 12.9 | 637 | 635 |
| Compound AN |  | C33H40N6O6 | 12.6 | | 657 |
| Compound AO |  | C33H40N6O6 | 11.3 | 617 | 615 |
| Compound AP |  | C34H41N5O6 | 14.5 | 616 | 614 |
| Compound AQ |  | C35H42BrN5O7 | 15.5 | 738/740 | 736/739 |
| Compound AR |  | C34H40ClN5O6 | 15 | 650 | 648 |
| Compound AS |  | C34H47N5O6 | 15.5 | 622 | 620 |
| Compound AT |  | C32H45N5O6 | 14.6 | 596 | 594 |

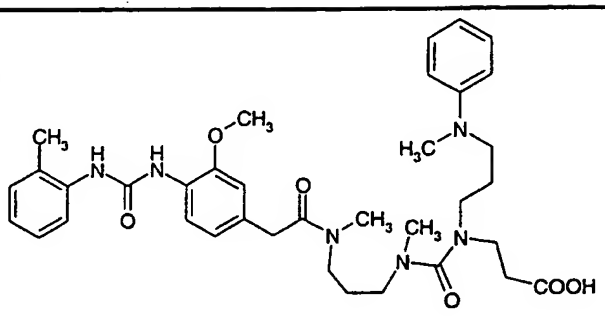
| | | | | | |
|---|---|---|---|---|---|
| Compound AU |  | C36H45N5O8 | 14.5 | 676 | 674 |
| Compound AV |  | C37H47N5O8 | 14.9 | 690 | 688 |
| Compound AW |  | C37H47N5O8 | 14.9 | 690 | 688 |
| Compound AX |  | C32H39N5O7 | 11.9 | | 638 |
| Compound AY |  | C35H43N5O7 | 14.6 | 646 | 645 |
| Compound AZ |  | C35H43N5O7 | 11.9 | | 644 |
| Compound BA |  | C35H41N5O8 | 11.9 | | |
| Compound BB |  | C35H43N5O6 | 14.9 | 630 | 628 |
| Compound BC |  | C35H40F3N5O6 | 15.8 | 684 | 682 |
| Compound BD |  | C36H45N5O8 | 11.9 | | |
| Compound BE |  | C34H48N6O6 | 11.7 | 637 | |
| Compound BF |  | C33H46N6O6 | 12.3 | 623 | |

| | | | | | |
|---|---|---|---|---|---|
| Compound BG |  | C36H52N6O6 | 11.7 | 665 | 664 |
| Compound BH |  | C36H45N5O6 | 15.4 | 644 | 642 |
| Compound BI |  | C36H46N6O6 | 11.9 | | 657 |

By proceeding in a similar manner to Example 1(a) above but using N-(3-aminopropyl)-N-methylaniline instead of 1-(3-aminopropyl)-2-pyrrolidinone there was prepared 3-{(4-{[3-methoxy-4-(3-o-tolyl-ureido)-phenyl]-acetyl}-[1,4]diazepane-1-carbonyl)-[3-(methyl-phenyl-amino)-propyl]-amino}-propionic acid (Compound LM). HPLC(Method B): $R_T$=10.4 minutes. MS(ES) : 657[(M-H)$^-$].

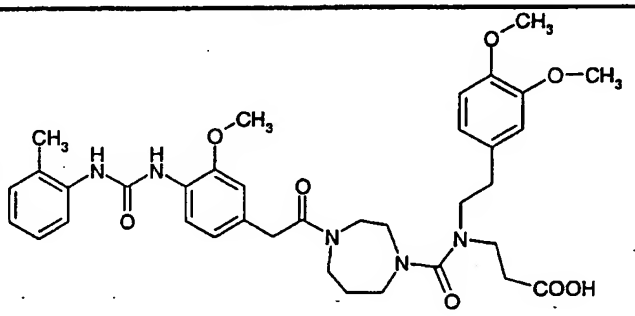
| | |
|---|---|
| Compound LM |  |

By proceeding in a similar manner to Example 1(a) above but using N,N'-dimethyl-1,3-propanediamine instead of homopiperazine and 3-(methyl-phenyl-amino)-propylamine instead of 1-(3-aminopropyl)-2-pyrrolidinone there was prepared 3-{3-[3-({[3-methoxy-4-(3-o-tolyl-ureido)-phenyl]-acetyl}-methyl-amino)-propyl]-3-methyl-1-[3-(methyl-phenyl-amino)-propyl]-ureido}-propionic acid (Compound LN). HPLC(Method B): $R_T$=10.2 minutes. MS(ES) : 659[(M-H)$^-$].

| | |
|---|---|
| Compound LN |  |

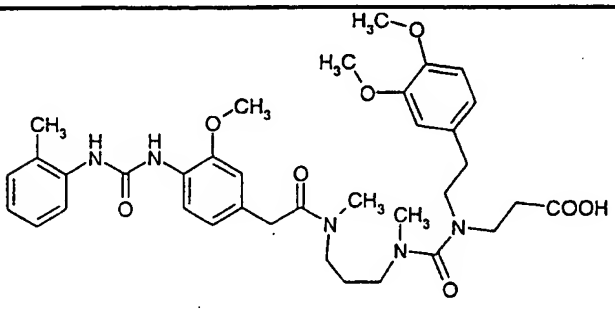
By proceeding in a similar manner to Example 1(a) above but using 2-(3,4-dimethoxy-phenyl)-ethylamine instead of 1-(3-aminopropyl)-2-pyrrolidinone there was prepared 3-[[2-(3,4-dimethoxy-phenyl)-ethyl]-(4-{[3-methoxy-4-(3-o-tolyl-ureido)-phenyl]-acetyl}-[1,4]diazepane-1-carbonyl)-amino]-propionic acid (Compound LO). HPLC(Method B): $R_T$=10.8 minutes.

MS(ES) : 674[(M-H)$^-$].

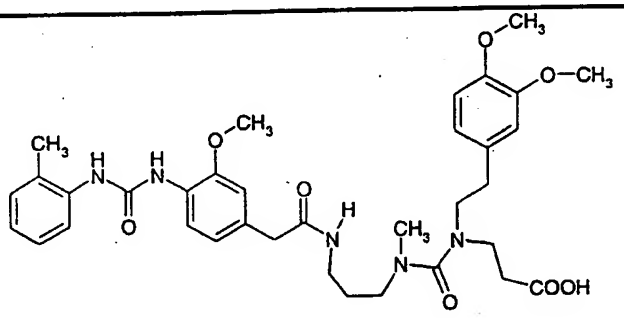
| | |
|---|---|
| Compound LO |  |

By proceeding in a similar manner to Example 1(a) above but N,N'-dimethyl-1,3-propanediamine instead of 1-(3-aminopropyl)-2-pyrrolidinone there was prepared 3-{1-[2-(3,4-Dimethoxy-phenyl)-ethyl]-3-[3-({[3-methoxy-4-(3-o-tolyl-ureido)-phenyl]-acetyl}-methyl-amino)-propyl]-3-methyl-ureido}-propionic acid (Compound LP). HPLC(Method B): $R_T$=10.8 minutes.

MS(ES) : 676[(M-H)$^-$].

| | |
|---|---|
| Compound LP |  |

By proceeding in a similar manner to Example 1(a) above but using 3,4-dimethoxy-3-(N-methyl-3-aminopropylimino)benzene (Reference Example 1) instead of 1-(3-aminopropyl)-2-pyrrolidinone (the resulting imine was then deprotected as described in Example 8 Step 4) and N-methyl-1,3-propanediamine instead of homopiperazine there was prepared 3-[1-[2-(3,4-dimethoxy-phenyl)-ethyl]-3-(3-{2-[3-methoxy-4-(3-o-tolyl-ureido)-phenyl]-acetylamino}-propyl)-3-methyl-ureido]-propionic acid (Compound LQ). HPLC(Method B): $R_T$=15.2 minutes. MS(ES) : 662[(M-H)$^-$].

| | |
|---|---|
| Compound LQ |  |

## EXAMPLE 2

Compounds BJ to DB

(a) Step 1. Wang resin (Advanced ChemTech, 10g) was placed in a flask and treated with a solution of 3-(9-fluorenylmethoxycarbonyl)butanoic acid (9.75g) in dimethylformamide (200ml) then with pyridine (4.52ml) and then with 2,6-dichlorobenzoyl chloride (4.3ml). The flask was shaken gently at ambient temperature for 18 hours then the resin was filtered and then washed three times with 50ml portions each of dimethylformamide, tetrahydrofuran, dichloromethane and diethyl ether, and then dried under vacuum.

Step 2. The resin from Step 1 (900mg, 0.79mmol/g loading) was placed in a flask and treated with 20% piperidine in dimethylformamide (20ml). The mixture was shaken for 2 minutes and drained. This process was repeated twice and then the resin was washed three times with 20ml portions of dimethylformamide, tetrahydrofuran and then a mixture of dichloromethane and tetrahydrofuran (1:1 v/v).

Step 3. The resin from Step 2 was swelled in a mixture of dichloromethane and tetrahydrofuran (20ml, 1:1, v/v) and then treated successively with diisopropylethylamine (1.23ml) and then 4-nitrophenylchloroformate. The mixture was gently agitated for 1 hour, then washed four times with a mixture of dichloromethane and tetrahydrofuran (1:1, v/v) and then sucked dry. A

solution of homopiperazine (0.71g) and triethylamine (0.67ml) in dimethylformamide (20ml) was added to the resin. After gently agitating the mixture for 1 hour the resin was drained and then washed three times with 20ml portions of dimethylformamide, tetrahydrofuran, a mixture of dichloromethane and tetrahydrofuran (1:1, v/v) and then dichloromethane, then dried under vacuum.

Step 4. The resin from Step 3 was treated with a solution of 3-methoxy-4-[3-(2-methylphenyl)ureido]phenylacetic acid (1.24g, prepared as described in Example 52B of International Patent Application Publication No. WO 96/22966), O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (1.19g) and diisopropylethylamine (1.65ml) in dimethylformamide (10ml). After gentle agitation for 3.5 hours the resin was drained, then washed three times with dimethylformamide, methanol, tetrahydrofuran and then dichloromethane, and then dried under vacuum.

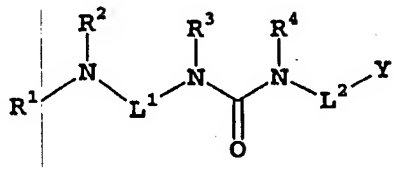
Step 5. The resin from Step 4 was treated with a mixture of trifluoroacetic acid and dichloromethane (15ml, 1:1, v/v) and allowed to stand for 1 hour with occasional agitation. The resin was drained, washed twice with a mixture of trifluoracetic acid and dichloromethane (5ml, 1:1, v/v) and the combined filtrates evaporated to dryness. The residue was triturated with diethyl ether to give 3-{[(4-{[3-methoxy-4-(2-methylphenylureido)-phenyl]-acetyl}-homopiperazin-1-yl)-carbonyl]-amino}-butanoic acid (Compound BJ) as a light brown solid (0.25g), m.p. >250°C with decomposition. MS: $MH^+$496.

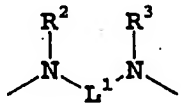
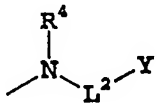
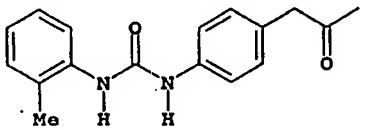
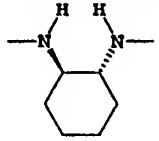
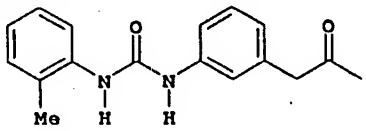
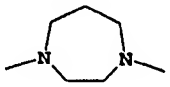
(b) By proceeding in a similar manner to Example 2(a) but using the appropriate protected amino-acid in step 1, the appropriate amine in step 3 and the appropriate acid is step 4, there was prepared Compounds BK to CR in Table 3.

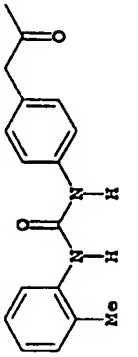
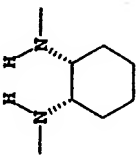
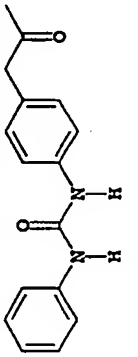
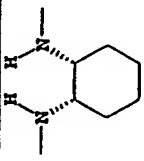
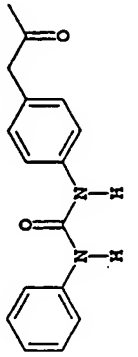
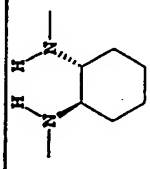
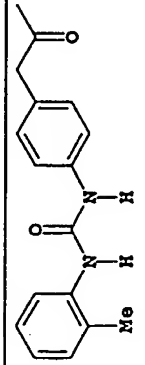
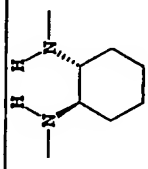
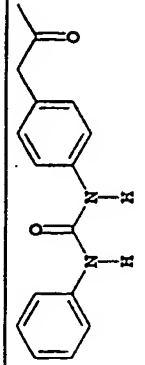
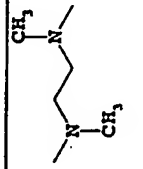
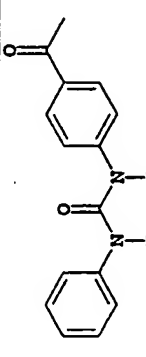
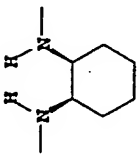
(c) By proceeding in a similar manner to Example 2(a) but using Rink amide resin and N-α-(9-fluorenylmethoxycarbonyl)-aspartic acid α-t-butyl ester in step 1, there was prepared 3-aminocarbonyl-3-{[(4-{[4-(2-methylphenylureido)-phenyl]-acetyl}-homopiperazin-1-yl)-carbonyl]-amino}-propanoic acid, Compound CS.

(d) By proceeding in a similar manner to Example 2(a) but using the appropriate amine in step 3 and the appropriate acid is step 4, there was prepared Compounds CT to DB in Table 4.

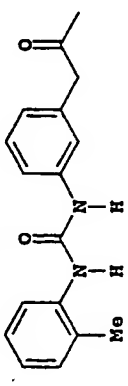
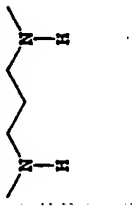
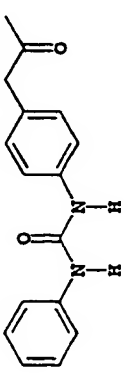
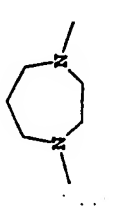
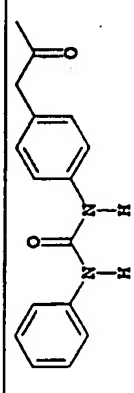
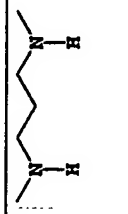
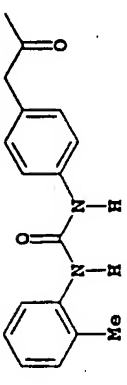
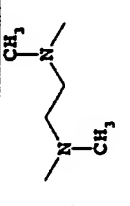
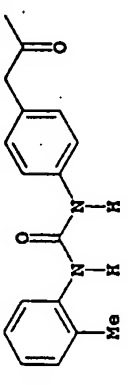
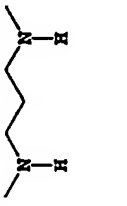
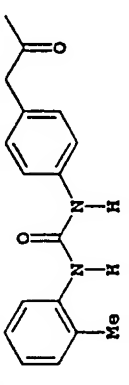
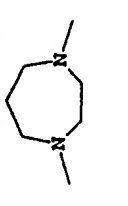
TABLE 3



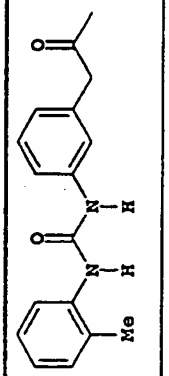
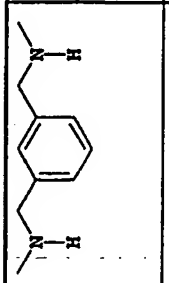
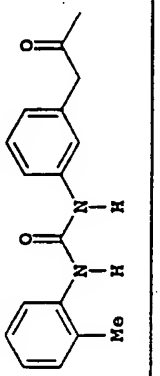
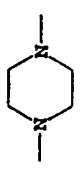
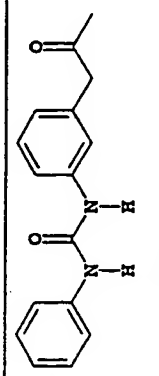
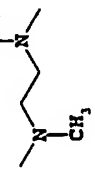
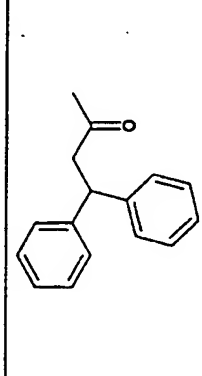
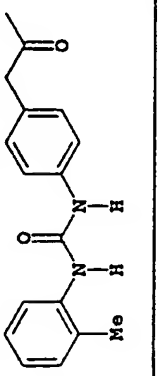
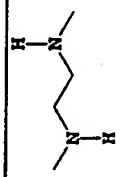
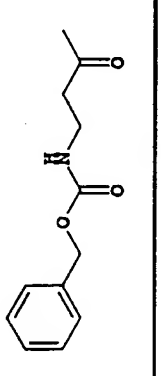
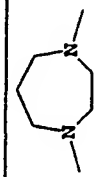
| Compound number | $R^1$ |  |  | Molecular formula | MS(ES) $MH^+$ (100% peak) |
|---|---|---|---|---|---|
| Compound BK |  |  | -NHCH($CH_3$)$CH_2CO_2H$ | $C_{27}H_{35}N_5O_5$ | 510 (510) |
| Compound BL |  |  | -NHCH($CH_3$)$CH_2CO_2H$ | $C_{26}H_{33}N_5O_5$ | 496 (202) |

| | | | | | |
|---|---|---|---|---|---|
| Compound BM |  |  | -NHCH$_2$CH$_2$CO$_2$H | C26H33N5O5 | 496 (496) |
| Compound BN |  |  | -NHCH(CH$_3$)CH$_2$CO$_2$H | C26H33N5O5 | 496 (496) |
| Compound BO |  |  | -NHCH(CH$_3$)CH$_2$CO$_2$H | C26H33N5O5 | 496 (496) |
| Compound BP |  |  | -NHCH(CH$_3$)CH$_2$CO$_2$H | C27H35N5O5 | 510 (510) |
| Compound BQ |  |  | (R) -NHCH(CH$_3$)CH$_2$CO$_2$H | C24H31N5O5 | 470 (470) |
| Compound BR |  |  | -NHCH(CH$_3$)CH$_2$CO$_2$H | C25H31N5O5 | 482 (373) |

| | | | | | |
|---|---|---|---|---|---|
| Compound BS |  |  | -NHCH$_2$CH$_2$CO$_2$H | C24H32N5O5 | 470 (470) |
| Compound BT |  |  | (R) -NHCH(CH$_3$)CH$_2$CO$_2$H | C23H29N5O5 | 456 (456) |
| Compound BU |  |  | -NHCH(CH$_3$)CH$_2$CO$_2$H | C22H27N5O5 | 442 (373) |
| Compound BV |  |  | (R) -NHCH(CH$_3$)CH$_2$CO$_2$H | C25H333N5O5 | 484 (484) |
| Compound BW |  |  | -NHCH(CH$_3$)CH$_2$CO$_2$H | C22H31ClN4O6 | - (435) |
| Compound BX |  |  | (R) -NHCH(CH$_3$)CH$_2$CO$_2$H | C26H32N5O5 | 496 (496) |

| | | | | | |
|---|---|---|---|---|---|
| Compound BY |  |  | -NHCH$_2$CH$_2$CH$_2$CO$_2$H | C24H31N5O5 | 470 (470) |
| Compound BZ |  |  | (R) -NHCH(CH$_3$)CH$_2$CO$_2$H | C25H31N5O5 | 482 (482) |
| Compound CA |  |  | (R) -NHCH(CH$_3$)CH$_2$CO$_2$H | C23H29N5O5 | 456 (456) |
| Compound CB |  |  | -NHCH$_2$CH$_2$CH$_2$CO$_2$H | C25H33N5O5 | 484 (484) |
| Compound CC |  |  | -NHCH$_2$CH$_2$CO$_2$H | C23H29N5O5 | 456 (456) |
| Compound CD |  |  | -NHCH$_2$CH$_2$CH$_2$CO$_2$H | C26H33N5O5 | 496 (496) |

| | | | | | |
|---|---|---|---|---|---|
| Compound CE |  |  | (R) -NHCH(CH$_3$)CH$_2$CO$_2$H | C21H25N5O5 | 428 (428) |
| Compound CF |  |  | -NHCH(CH$_3$)CH$_2$CO$_2$H | C29H33N5O5 | 532 (532) |
| Compound CG |  |  | -NHCH$_2$CO$_2$H | C25H31N5O5 | 482 (482) |
| Compound CH |  |  | -NHCH(Ph)CH$_2$CO$_2$H | C24H29ClN4O6 | 506 (491) |
| Compound CI |  |  | -NHCH(CONH$_2$)CH$_2$CO$_2$H | C14H20N4O5S | 357 (357) |
| Compound CJ |  |  | (R) -NHCH(CH$_3$)CH$_2$CO$_2$H | C22H31ClN4O6 | 483 (469) |

| | | | | | |
|---|---|---|---|---|---|
| Compound CK |  |  | -NHCH$_2$CH$_2$CH$_2$CO$_2$H | C29H33N5O5 | 532 (532) |
| Compound CL |  |  | -NHCH$_2$CH$_2$CO$_2$H | C24H29N5O5 | 468 (468) |
| Compound CM |  |  | (R) -NHCH(CH$_3$)CH$_2$CO$_2$H | C24H31N5O5 | 470 (470) |
| Compound CN |  |  | (R) -NHCH(CH$_3$)CH$_2$CO$_2$H | C25H31N3O4 | 438 (438) |
| Compound CO |  |  | -NHCH$_2$CH$_2$CO$_2$H | C22H27N5O5 | 442 (442) |
| Compound CP |  |  | (R) -NHCH(CH$_3$)CH$_2$CO$_2$H | C21H30N4O6 | 435 (435) |

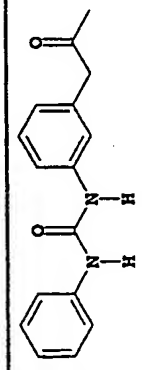
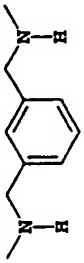
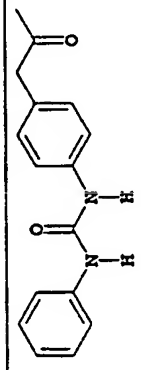
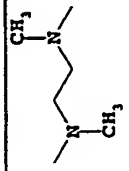
| | | | | | |
|---|---|---|---|---|---|
| Compound CQ |  |  | -NHCH(CH$_3$)CH$_2$CO$_2$H | C27H29N5O5 | 504 (504) |
| Compound CR |  |  | -NHCH$_2$CH$_2$CO$_2$H | C23H29N5O5 | 456 (456) |

TABLE 4



| Compound number | R1- | | | Molecular formula | MS(ES) MH+ (100% peak) |
|---|---|---|---|---|---|
| Compound CT |  |  | (R) -NHCH(CH3)CH2CO2H | C21H29ClN4O6 | 469 (455) |
| Compound CU |  |  | -NHCH(CONH2)CH2CO2H | C26H32N6O6 | 525 (525) |
| Compound CV |  |  | -NHCH(CONH2)CH2CO2H | C25H32N6O6 | 513 (513) |

| | | | | | |
|---|---|---|---|---|---|
| Compound CW |  |  | -NHCH(CONH$_2$)CH$_2$CO$_2$H | C27H34N6O6 | 539 (539) |
| Compound CX |  |  | -NHCH(CONH$_2$)CH$_2$CO$_2$H | C23H30N6O6 | 485. (485) |
| Compound CY |  |  | -NHCH(CONH$_2$)CH$_2$CO$_2$H | C25H31N5O5 | 511 (373) |
| Compound CZ |  |  | -NHCH(CONH$_2$)CH$_2$CO$_2$H | C26H32N6O6 | 525 (373) |
| Compound DA |  |  | -NHCH(CONH$_2$)CH$_2$CO$_2$H | C20H25N5O7 | 448 (448) |
| Compound DB |  |  | -NHCH(CONH$_2$)CH$_2$CO$_2$H | C19H27N5O5 | 406 (435) |

## EXAMPLE 3

Compounds DC to EZ

Step 1. (a) A suspension of Wang resin (15g , Advanced ChemTech) in dichloromethane (200ml) was treated with diisopropylethylamine (9ml) then with acryloyl chloride (4.5ml) and then kept at ambient temperature for 3 hours with occasional agitation. The mixture was filtered, then washed three times with 50ml portions each of dichloromethane, tetrahydrofuran, dimethylformamide, tetrahydrofuran and dichloromethane, and then dried under vacuum to give acrylate-loaded Wang resin.

(b) Replacing the acryloyl chloride with methacryloyl chloride gave methacrylate-loaded Wang resin.

(c) Replacing the acryloyl chloride with crotonyl chloride gave and crotonate-loaded Wang resin.

Step 2. The resins from Step 1(a), (b) and (c) were treated with methylamine (8M solution in ethanol), or the appropriately substituted amine, in a similar manner to that described in Example 1 Step 2.

Step 3. The resins from Step 2 immediately above were treated in a similar manner to that described in Example 1 Step 3 but using (i) a solution of phosgene in toluene (1.93M) to replace the triphosgene, (ii) diisopropylethylamine to replace the pyridine and (iii) homopiperazine or the appropriate diamine.

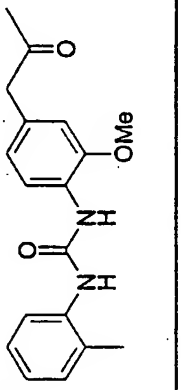
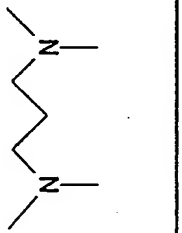
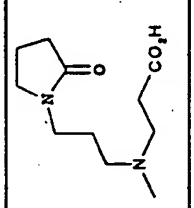
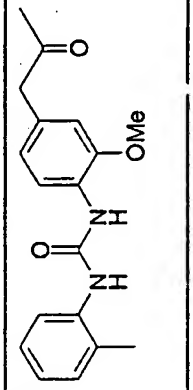
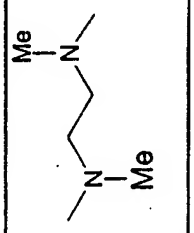
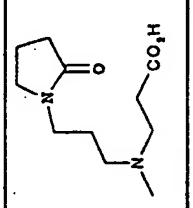
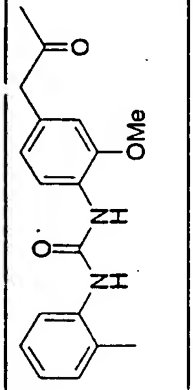
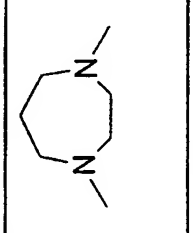
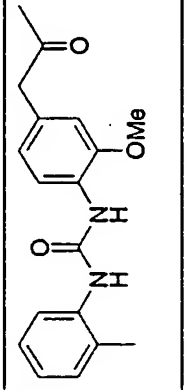
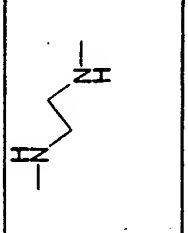
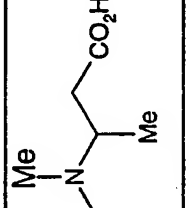
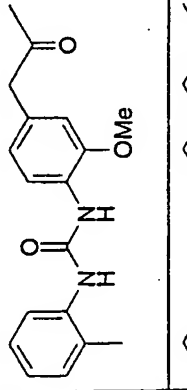
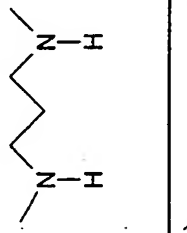
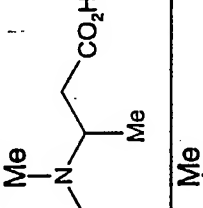
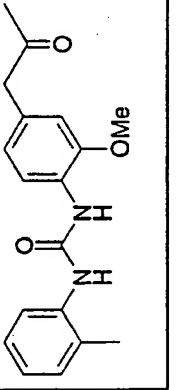
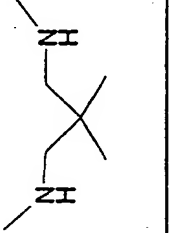
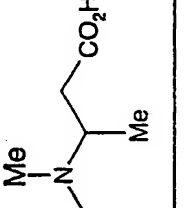
Step 4. The resins from Step 3 immediately above were treated in a similar manner to that described in Example 1 Step 4 using 3-methoxy-4-[3-(2-methylphenyl)ureido]phenylacetic acid or 3-methoxy-4-[3-(2-methylphenyl)ureido]phenylacetic acid.

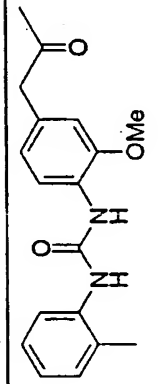
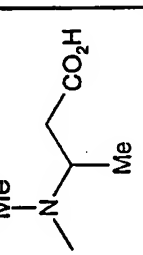
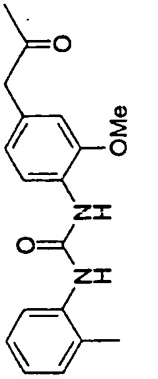
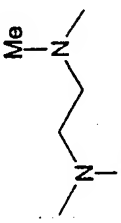
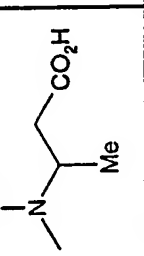
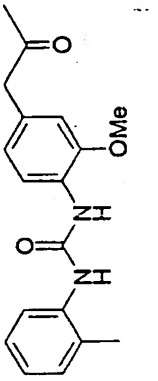
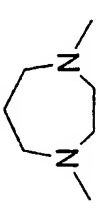
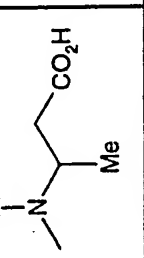
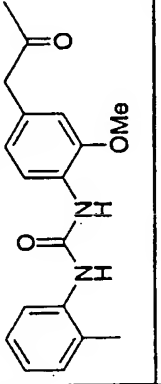
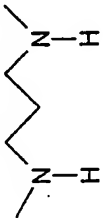
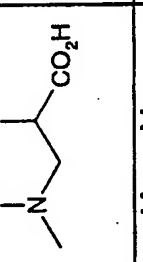
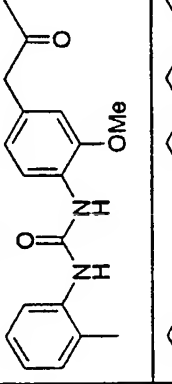
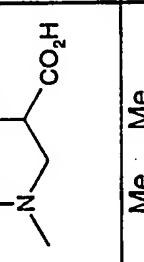
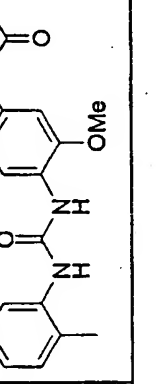
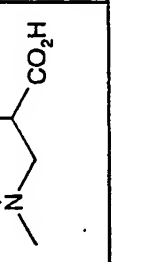
Step 5. The resins from Step 4 immediately above were treated in a similar manner to that described in Example 1 Step 5, but using a mixture of trifluoroacetic acid, dichloromethane and water (70:25:5, v/v/v), to give Compounds DC to EZ depicted in Table 5.

TABLE 5



| Compound Number | $R^1$ |  |  | Molecular formula | HPLC $R_T$ (minutes) | MS(ES) $(M+H)^+$ |
|---|---|---|---|---|---|---|
| Compound DC |  |  |  | C30H40N6O7 | 2.38 | 597 |
| Compound DD |  |  |  | C31H42N6O7 | 2.44 | 611 |
| Compound DE |  |  |  | C33H46N6O7 | 2.6 | 639, M |

| | | | | | | |
|---|---|---|---|---|---|---|
| Compound DF |  |  |  | C33H46N6O7 | 2.51 | 639 |
| Compound DG |  |  |  | C32H44N6O7 | 2.47 | 625 |
| Compound DH |  |  |  | C33H44N6O7 | 2.47 | 637, |
| Compound DI |  |  |  | C25H33N5O6 | 2.46 | 500 |
| Compound DJ |  |  |  | C26H35N5O6 | 2.51 | 514 |
| Compound DK |  |  |  | C28H39N5O6 | 2.71 | 542 |

| | | | | | |
|---|---|---|---|---|---|
| Compound DL |  |  |  | C28H39N5O6 | 2.69 | 542 |
| Compound DM |  |  |  | C27H37N5O6 | 2.62 | 528 |
| Compound DN |  |  |  | C28H37N5O6 | 2.62 | 540 |
| Compound DO |  |  |  | C26H35N5O6 | 2.51 | 514, |
| Compound DP |  |  |  | C28H39N5O6 | 2.73 | 542 |
| Compound DQ |  |  |  | C28H39N5O6 | 2.66 | 542 |

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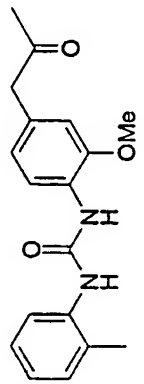
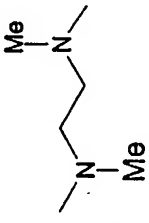
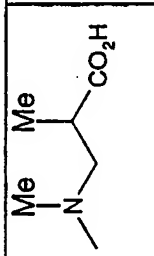
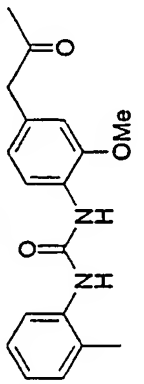
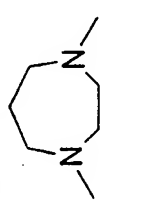
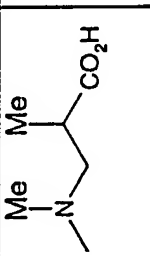
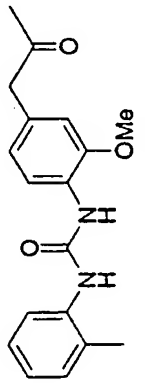
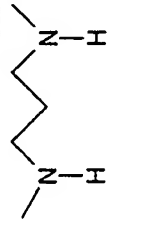
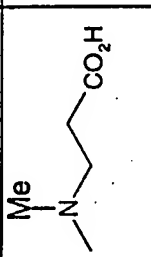
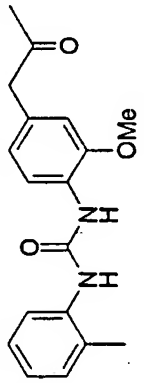
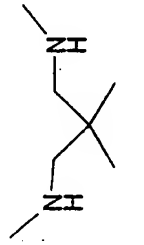
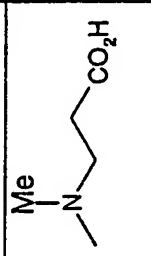
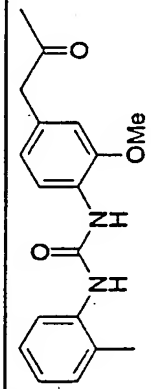
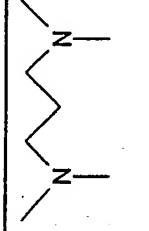
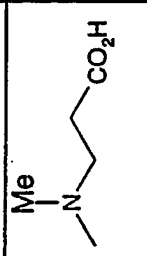
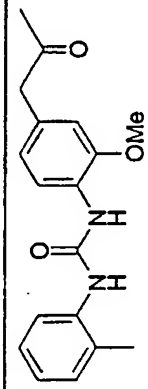
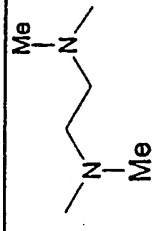
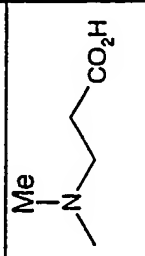
| Compound DR |  |  |  | C27H37N5O6 | 2.6 | 528 |
| Compound DS |  |  |  | C28H37N5O6 | 2.62 | 540, |
| Compound DT |  |  |  | C25H33N5O6 | 2.44 | 500 |
| Compound DU |  |  |  | C27H37N5O6 | 2.64 | 528 |
| Compound DV |  |  |  | C27H37N5O6 | 2.59 | 528 |
| Compound DW |  |  |  | C26H35N5O6 | 2.53 | 514 |

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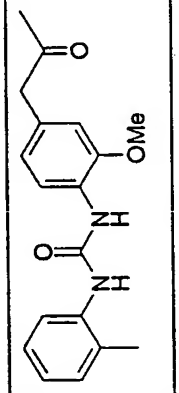
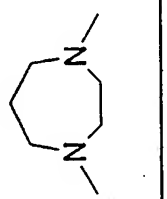
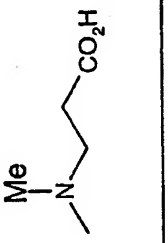
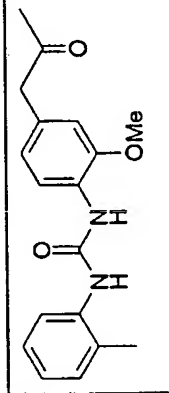
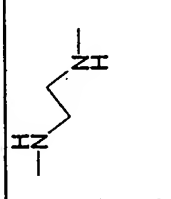
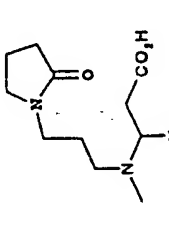
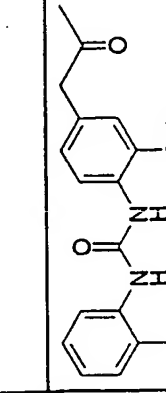
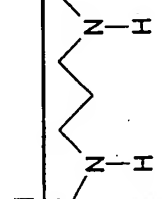
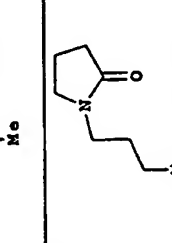
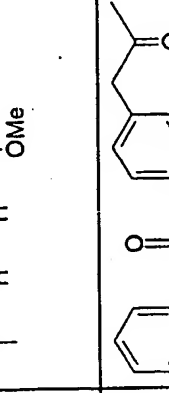
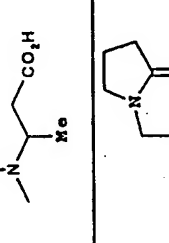
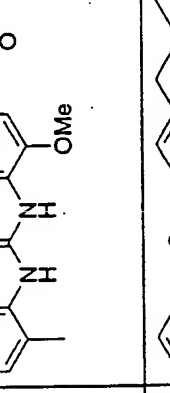
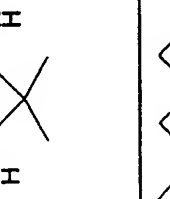
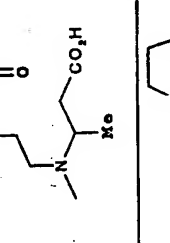
| Compound DX |  |  |  | C27H35N5O6 | 526 |
| Compound DY |  |  |  | C31H42N6O7 | 611 |
| Compound DZ |  |  |  | C32H44N6O7 | 625 |
| Compound EA |  |  |  | C34H48N6O7 | 653 |
| Compound EB |  |  |  | C34H48N6O7 | 653 |

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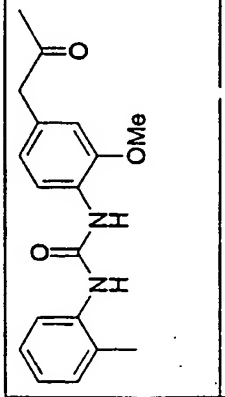
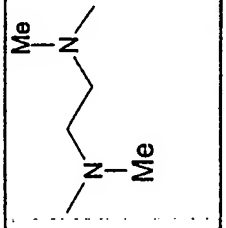
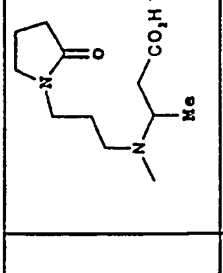
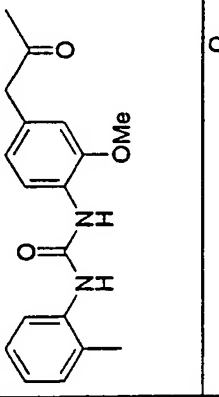
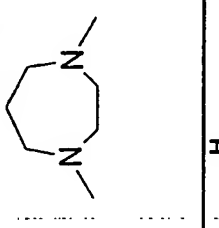
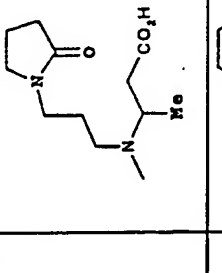
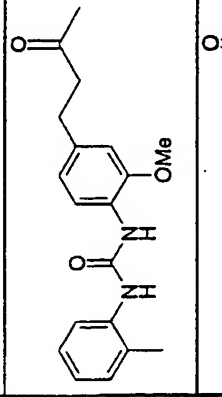
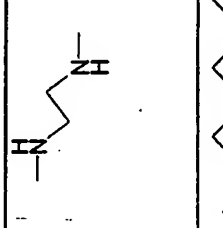
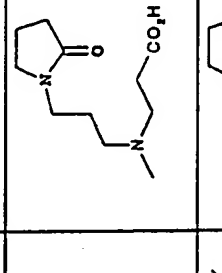
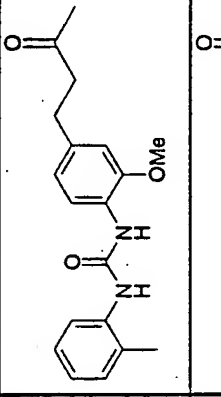
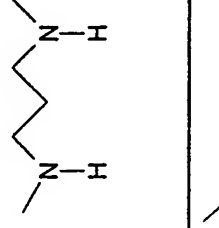
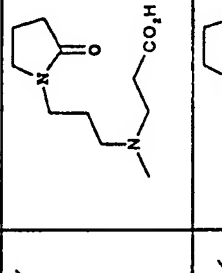
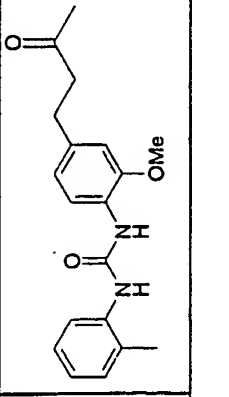
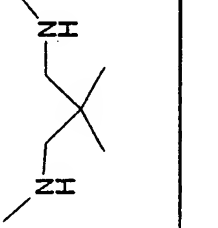
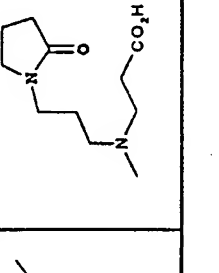
| Compound EC |  |  |  | C33H46N6O7 | 2.55 | 639 |
| Compound ED |  |  |  | C34H46N6O7 | 2.53 | 651 |
| Compound EE |  |  |  | C31H42N6O7 | 2.44 | 611 |
| Compound EF |  |  |  | C32H44N6O7 | 2.46 | 625 |
| Compound EG |  |  |  | C34H48N6O7 | 2.64 | 653 |

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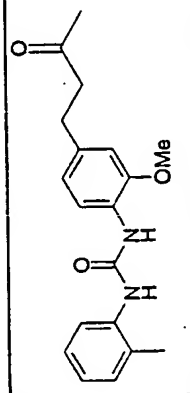
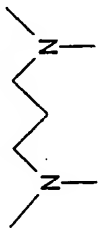
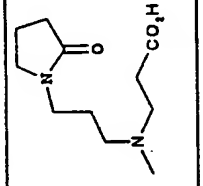
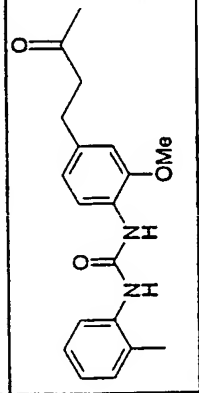
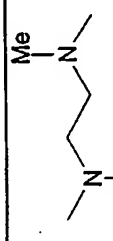
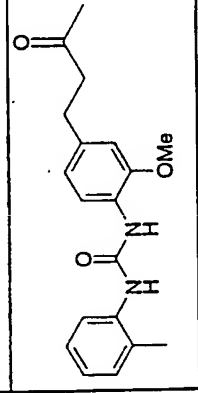
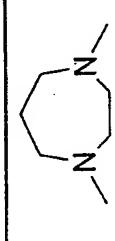
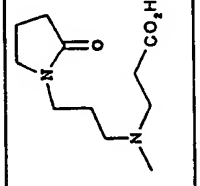
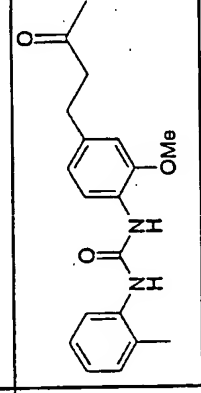
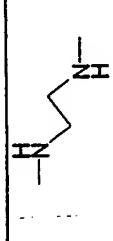
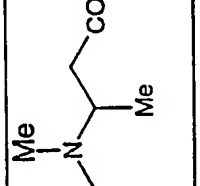
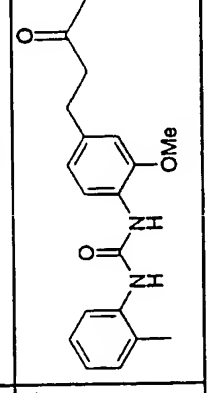
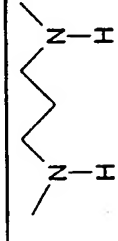
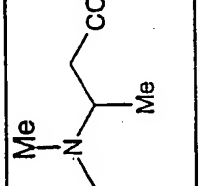
| Compound EH |  |  |  | C34H48N6O7 | 2.57 | 653 |
| Compound EI |  |  |  | C33H46N6O7 | 2.55 | 639 |
| Compound EJ |  |  |  | C34H46N6O7 | 2.57 | 651 |
| Compound EK |  |  |  | C26H35N5O6 | 2.51 | 514 |
| Compound EL |  |  |  | C27H37N5O6 | 2.56 | 528 |

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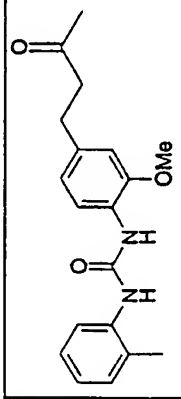
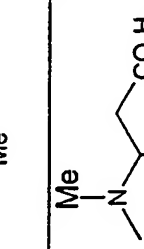
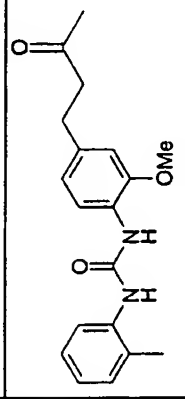
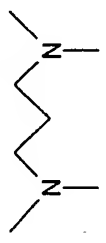
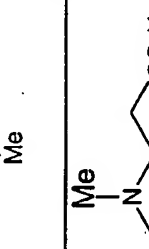
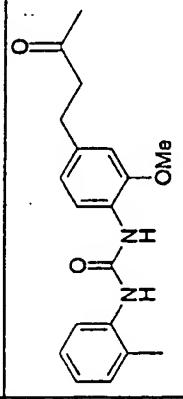
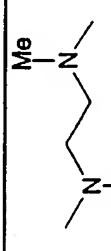
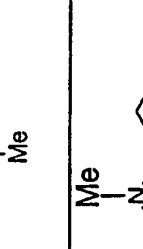
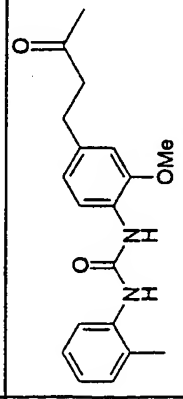
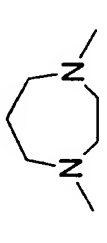
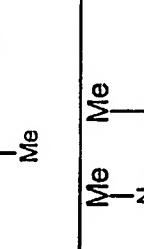
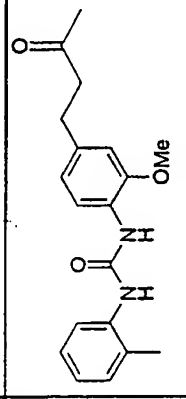
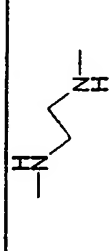
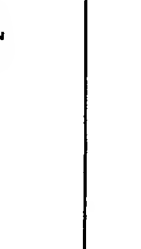
| Compound EM |  |  |  | C29H41N5O6 | 2.77 | 556 |
| Compound EN |  |  |  | C29H41N5O6 | 2.75 | 556 |
| Compound EO |  |  |  | C28H39N5O6 | 2.7 | 542 |
| Compound EP |  |  |  | C29H39N5O6 | 2.71 | 554 |
| Compound EQ |  |  |  | C26H35N5O6 | 2.51 | 514 |

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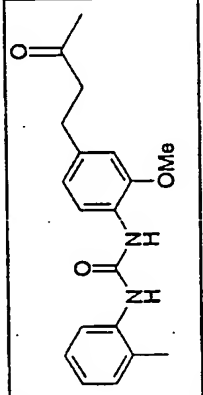
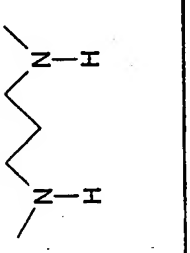
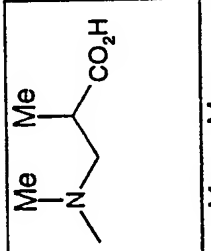
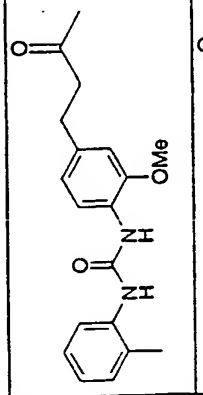
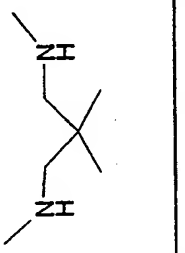
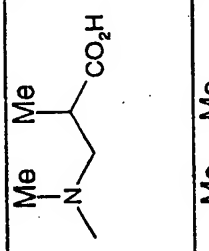
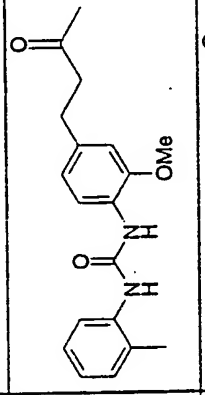
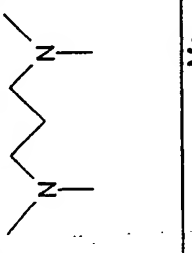
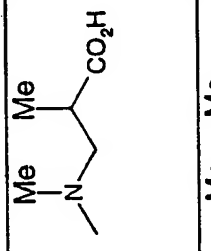
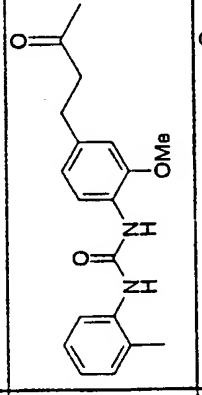
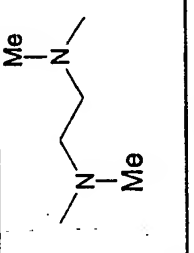
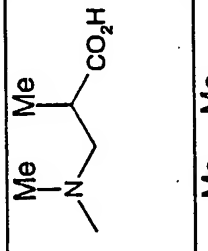
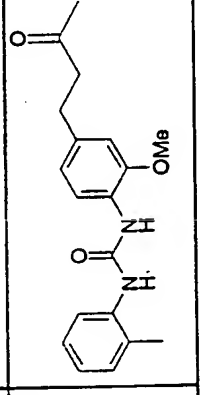
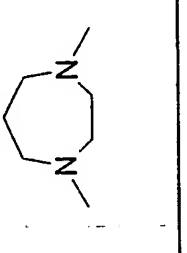
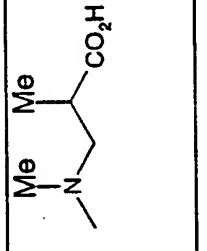
| Compound ER |  |  |  | C27H37N5O6 | 528 |
| Compound ES |  |  |  | C29H41N5O6 | 556 |
| Compound ET |  |  |  | C29H41N5O6 | 556 |
| Compound EU |  |  |  | C28H39N5O6 | 542 |
| Compound EV |  |  |  | C29H39N5O6 | 554 |

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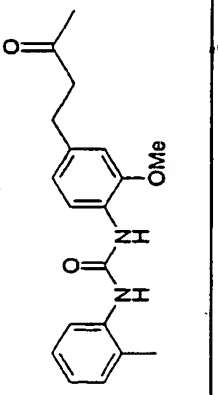
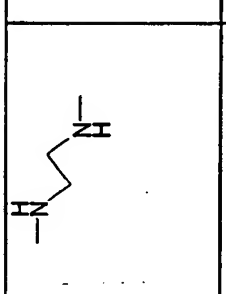
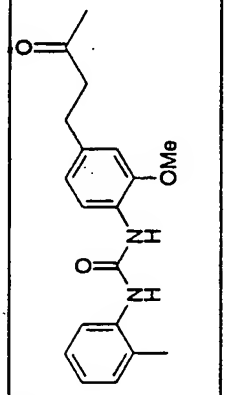
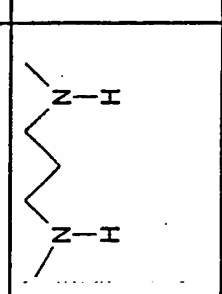
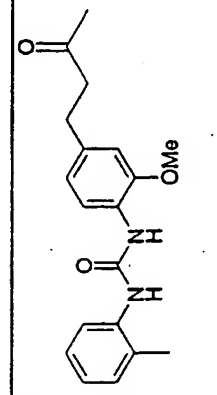
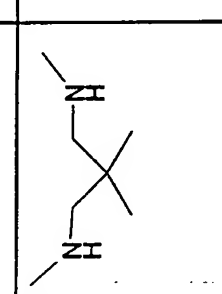
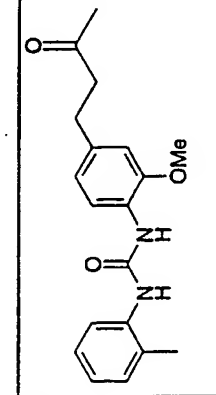
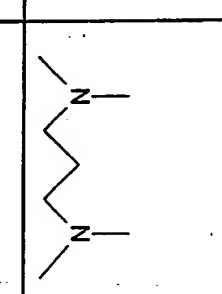
| Compound EW |  |  | C32H44N6O7 | 2.51 | 625 |
| Compound EX |  |  | C33H46N6O7 | 2.53 | 639 |
| Compound EY |  |  | C35H50N6O7 | 2.7 | 667 |
| Compound EZ |  |  | C35H50N6O7 | 2.66 | 667 |

## EXAMPLE 4

COMPOUNDS FA TO IB

Step 1. A stirred suspension of Wang resin (19.7g , 1.0m.mol./g) in dichloromethane (200ml), under a nitrogen atmosphere, was treated with a solution of triphenylphosphine dibromide (25g) in dichloromethane (200mL). After stirring for 16hours the reaction mixture was filtered and the modified resin was washed four times with dichloromethane, then with diethyl ether and then dried in vacuo.

Step2. (a) The resin (20g) from step 1 was swelled in dimethylformamide (140mL) then treated successively with cesium iodide (4.7g), 3-(9-fluorenylmethoxycarbonylamino)propanoic acid (8.4g) and diisopropylethylamine (4.7mL). The mixture was shaken for 24hours then filtered. The resin was washed three times with dimethylformamide, then with tetrahydrofuran, then with four alternating washes of dichloromethane and methanol, then twice with diethyl ether and then dried at 45°C in vacuo to give Wang resin loaded with a 3-(9-fluorenylmethoxycarbonylamino)propanoyl group, (0.67m.mol./g).

(b) By proceeding in a similar manner but using 3-(9-fluorenylmethoxycarbonylamino)-2-methylpropanoic acid there was prepared Wang resin loaded with a 3-(9-fluorenylmethoxycarbonylamino)-2-methylpropanoyl group.

(c) By proceeding in a similar manner but using N-α-(9-fluorenylmethoxycarbonyl)-L-asparagine there was prepared Wang resin loaded with a N-α-(9-fluorenylmethoxycarbonyl)-L-asparaginyl group.

(d) By proceeding in a similar manner but using N-α-(9-fluorenylmethoxycarbonyl)-L-aspartic acid there was prepared Wang resin loaded with a N-α-(9-fluorenylmethoxycarbonyl)-L-aspartyl group.

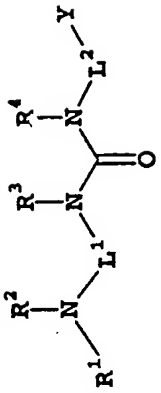
(e) By proceeding in a similar manner but using β-tert-butyl ester, S-3-(9-fluorenylmethoxycarbonylamino)-butanoic acid there was prepared Wang resin loaded with a β-tert-butyl ester, S-3-(9-fluorenylmethoxy-carbonylamino)butanoyl group.

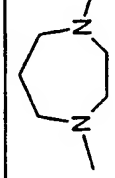
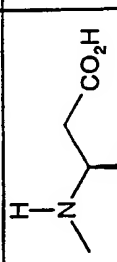
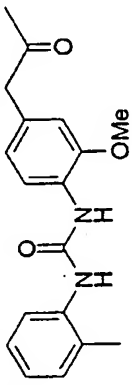
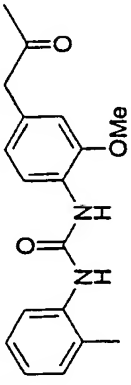
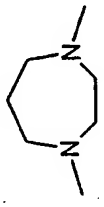
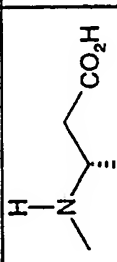
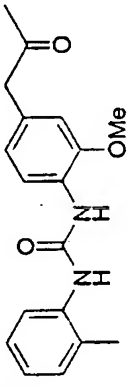
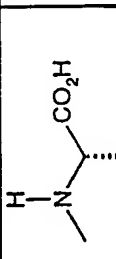
(f) By proceeding in a similar manner but using R-3-(9-fluorenylmethoxycarbonylamino)butanoic acid there was prepared Wang resin loaded with a R-3-(9-fluorenylmethoxycarbonylamino)butanoyl group.

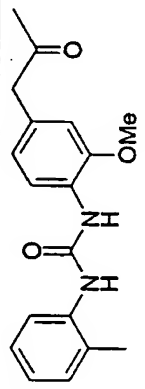
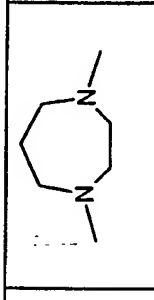
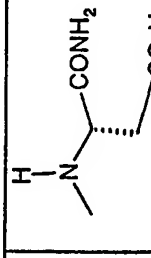
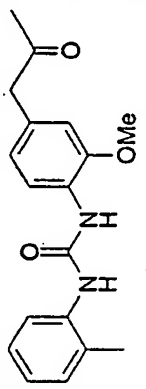
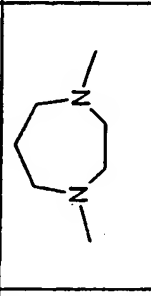
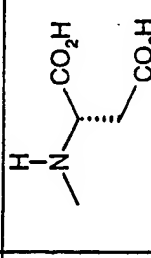
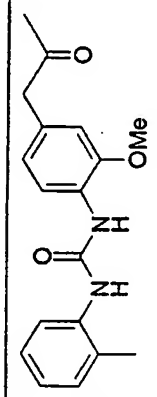
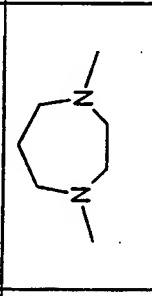
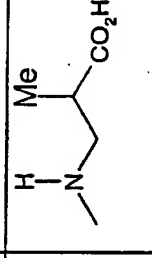
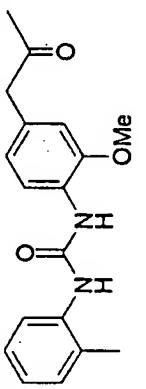
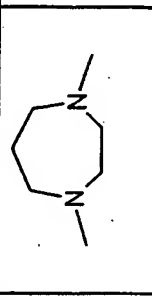
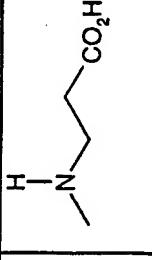
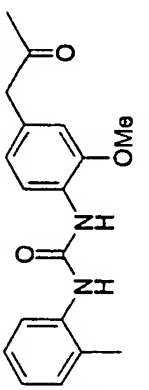
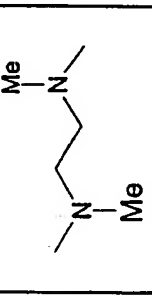
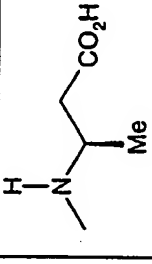
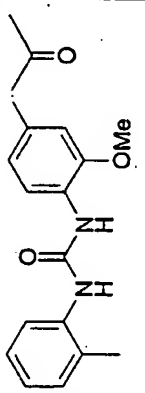
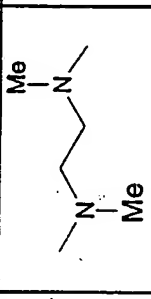
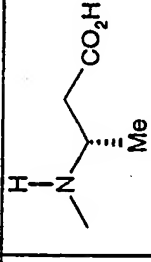
(g) Rink amide resin (4.5g, 0.54m.mol./g) was treated with an excess of a mixture of dimethylformamide and piperidine (4:1, v/v) for a short time. The resin was then washed six times with dimethylformamide and then sucked dry. The resin was resuspended in dimethylformamide (25mL) and then treated with diisopropylethylamine (5.08mL), N-α-(9-fluorenylmethoxycarbonyl)-L-aspartic acid, β-tert-butyl ester (5.0g) and a solution of O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (3.7g) in dimethylformamide (25mL). After shaking for 4hours the mixture was filtered, then washed three times with dimethylformamide and then twice with tetrahydrofuran. The resin was washed further with four alternating washes of dichloromethane and methanol, then twice with diethyl ether and then dried in vacuo to give Rink amide resin loaded with a β-tert-butyl ester, N-α-(9-fluorenylmethoxycarbonyl)-L-aspartyl group (0.58m.mol./g).

Step4. Using the resins from steps 2(a) to 2(g) and proceeding in a similar manner to that described in Example 2a steps 3 and 4, but using the appropriate diamines in step 3 and the appropriate acids in step4, then proceeding in a similar manner to that described in Example 3 step5 there was obtained the Compounds FA to IB depicted in Table 6.

TABLE 6



| Compound Number | $R^1$ |  |  | Molecular formula | HPLC $R_T$ (minutes) | MS $(M+H)^+$ |
|---|---|---|---|---|---|---|
| Compound FA |  |  |  | C27H35N5O6 | 3.01 | 526 |
| Compound FB |  |  |  | C27H35N5O6 | 3.01 | 526 |
| Compound FC |  |  |  | C27H34N6O7 | 2.79 | 555 |

| | | | | | | |
|---|---|---|---|---|---|---|
| Compound FD |  |  |  | C27H34N6O7 | 2.82 | 555 |
| Compound FE |  |  |  | C27H33N5O8 | 2.89 | 556 |
| Compound FF |  |  |  | C27H35N5O6 | 2.99 | 526 |
| Compound FG |  |  |  | C26H33N5O6 | 2.92 | 512 |
| Compound FH |  |  |  | C26H35N5O6 | 3.03 | 514 |
| Compound FI |  |  |  | C26H35N5O6 | 3.03 | 514 |

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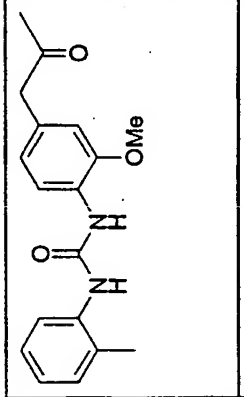
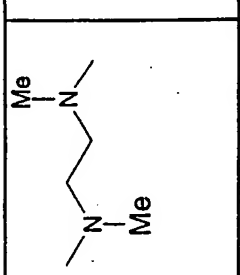
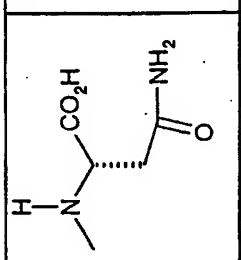
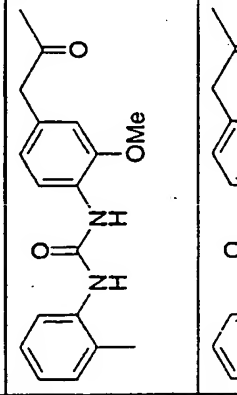
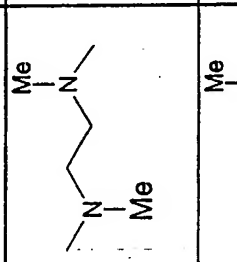
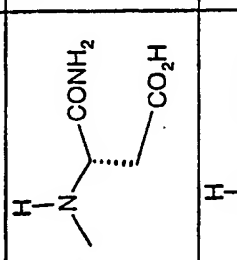
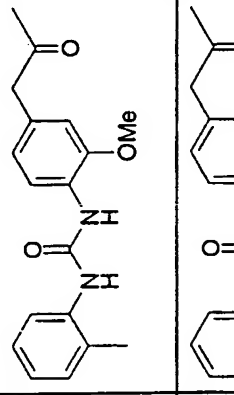
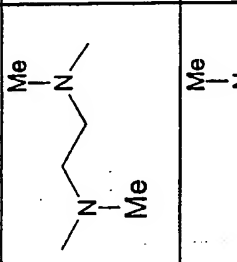
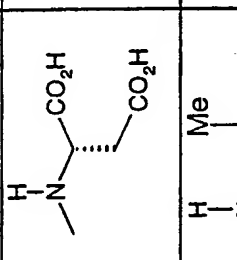
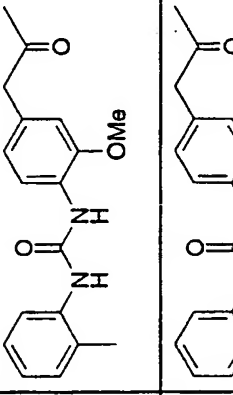
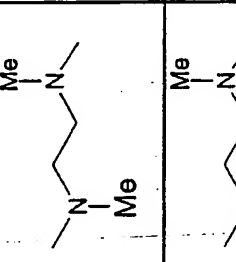
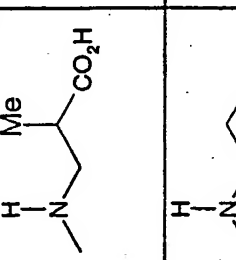
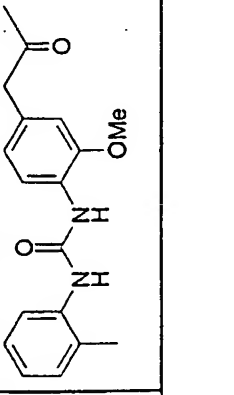
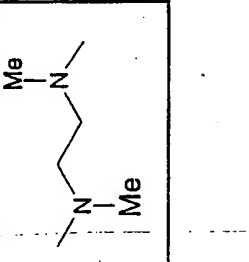
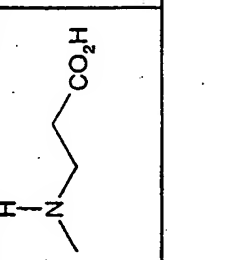
| Compound FJ |  |  |  | C26H34N6O7 | 2.8 | 543 |
| Compound FK |  |  |  | C26H34N6O7 | 2.84 | 543 |
| Compound FL |  |  |  | C26H33N5O8 | 2.9 | 544 |
| Compound FM |  |  |  | C26H35N5O6 | 3.01 | 514 |
| Compound FN |  |  |  | C25H33N5O6 | 2.93 | 500 |

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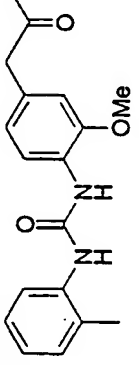
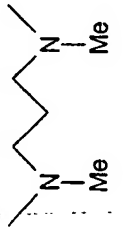
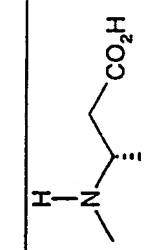
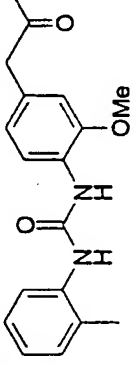
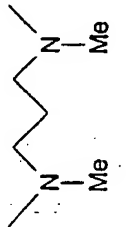
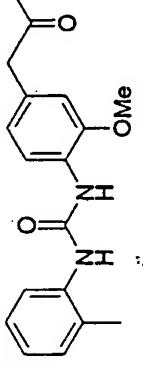
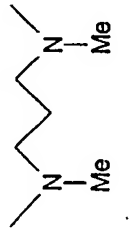
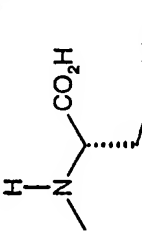
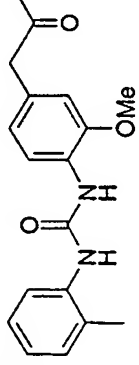
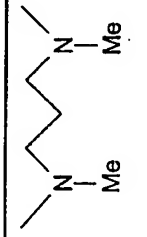
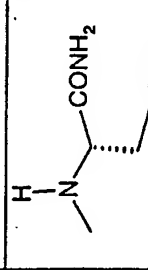
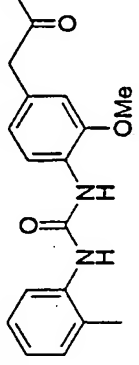
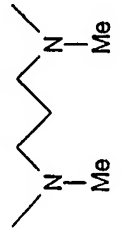
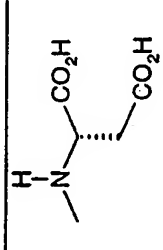
| Compound FO |  |  |  | C27H37N5O6 | 3.07 | 528 |
| Compound FP |  |  |  | C27H37N5O6 | 3.07 | 528 |
| Compound FQ |  |  |  | C27H36N6O7 | 2.85 | 557 |
| Compound FR |  |  |  | C27H36N6O7 | 2.88 | 557 |
| Compound FS |  |  |  | C27H35N5O8 | 2.95 | 558 |

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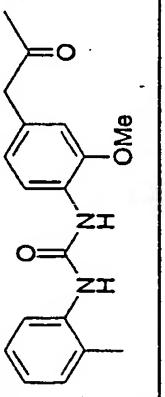
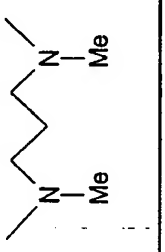
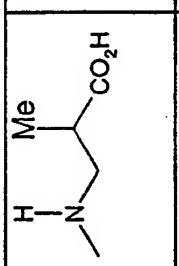
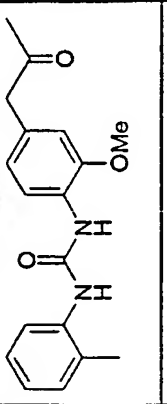
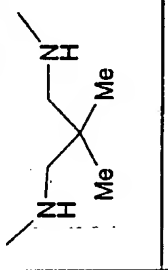
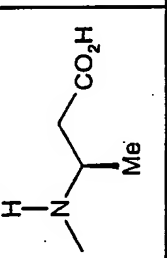
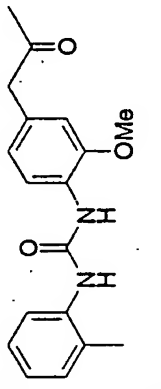
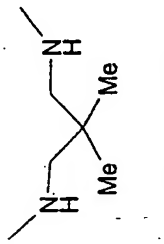
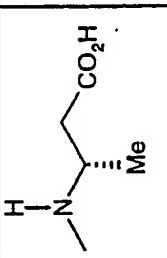
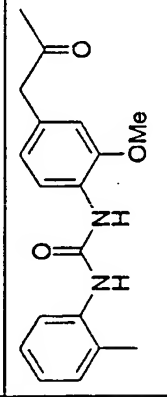
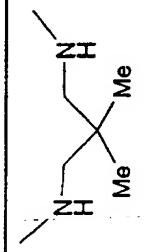
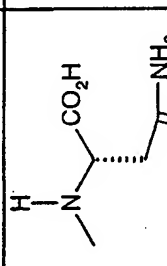
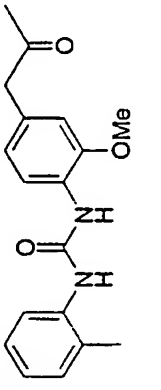
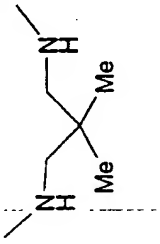
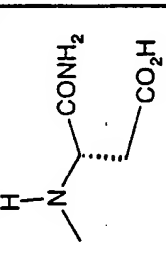
| Compound FT |  |  |  | C27H37N5O6 | 3.06 | 528 |
| Compound FU |  |  |  | C27H37N5O6 | 3.14 | 528 |
| Compound FV |  |  |  | C27H37N5O6 | 3.15 | 528 |
| Compound FW |  |  |  | C27H36N6O7 | 2.92 | 557 |
| Compound FX |  |  |  | C27H36N6O7 | 2.94 | 557 |

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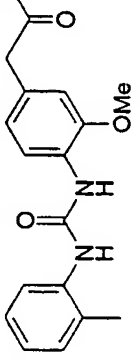
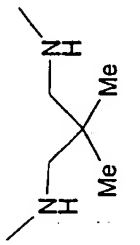
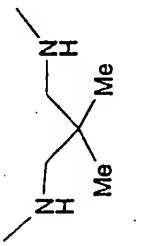
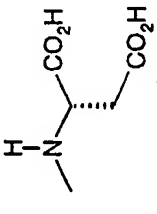
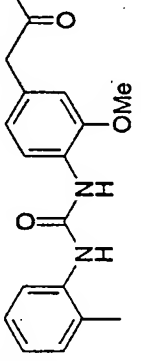
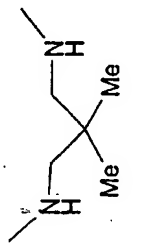
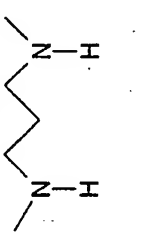
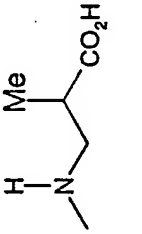
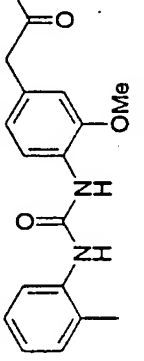
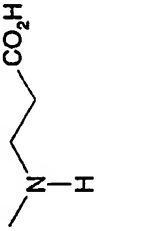
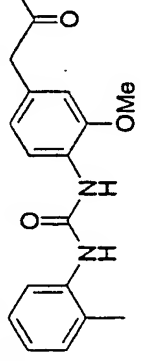
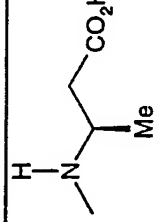
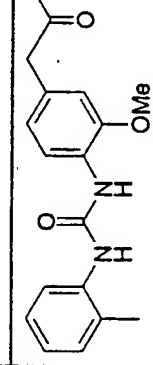
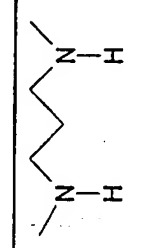
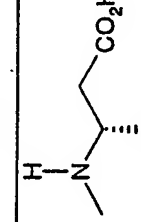
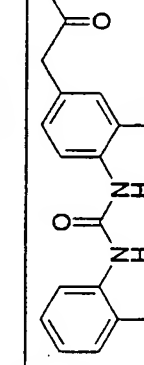
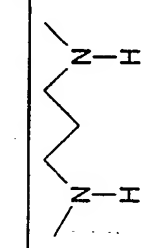
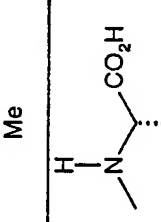
| Compound FY |  |  |  |  | C27H35N5O8 | 3.02 | 558 |
| Compound FZ |  |  |  |  | C27H37N5O6 | 3.15 | 528 |
| Compound GA |  |  |  |  | C26H35N5O6 | 3.06 | 514 |
| Compound GB |  |  |  |  | C25H33N5O6 | 2.95 | 500 |
| Compound GC |  |  |  |  | C25H33N5O6 | 2.95 | 500 |
| Compound GD |  |  |  |  | C25H32N6O7 | 2.77 | 529 |

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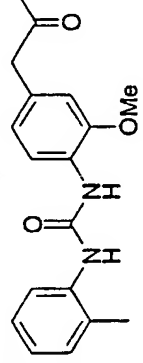
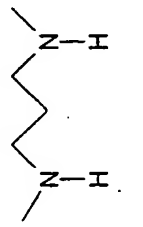
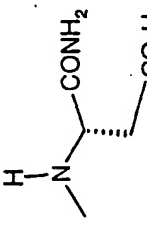
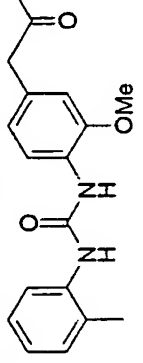
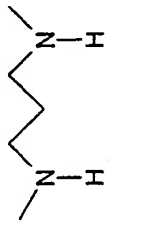
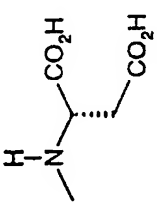
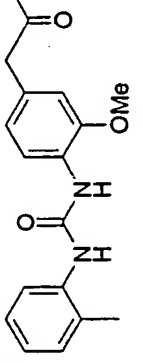
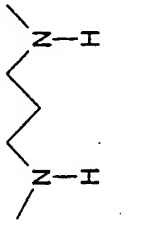
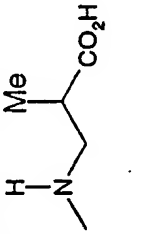
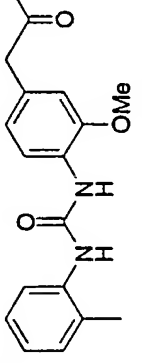
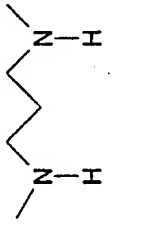
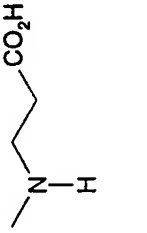
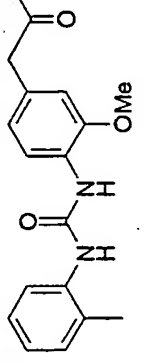
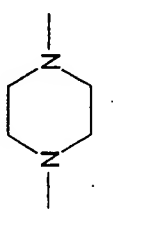
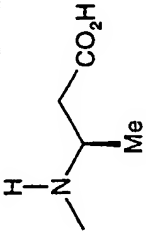
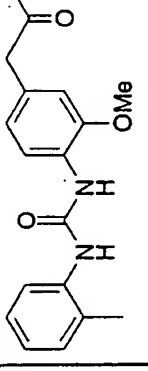
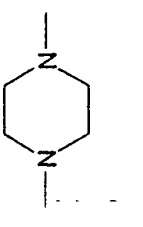
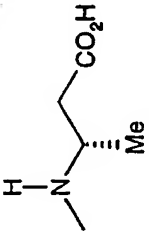
| Compound GE |  |  |  | C25H32N6O7 | 2.77 | 529 |
| Compound GF |  |  |  | C25H31N5O8 | 2.86 | 530 |
| Compound GG |  |  |  | C25H33N5O6 | 2.96 | 500, |
| Compound GH |  |  |  | C24H31N5O6 | 2.88 | 486 |
| Compound GI |  |  |  | C26H33N5O6 | 2.99 | 512 |
| Compound GJ |  |  |  | C26H33N5O6 | 2.99 | 512 |

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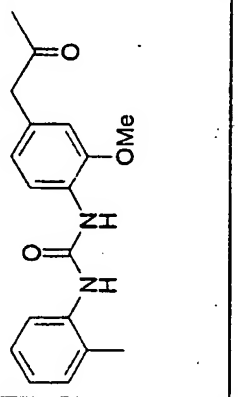
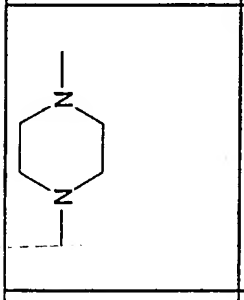
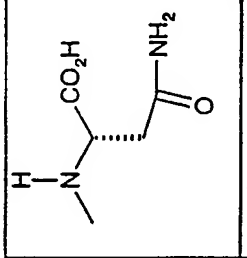
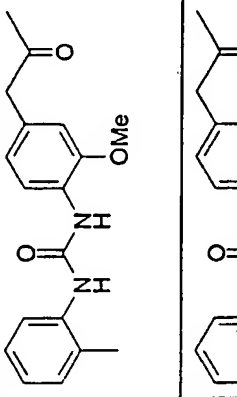
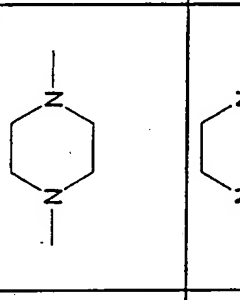
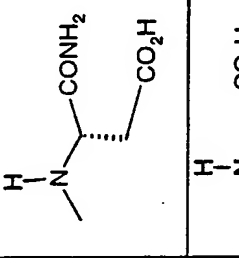
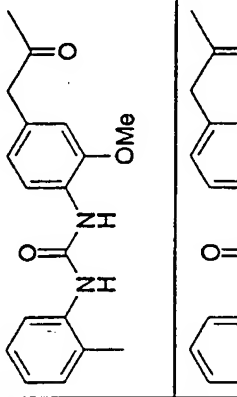
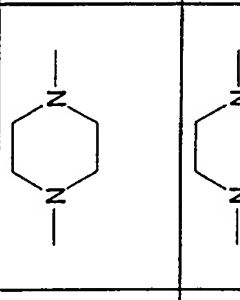
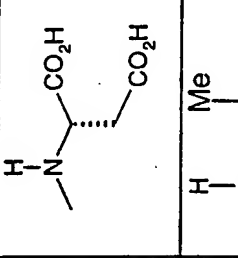
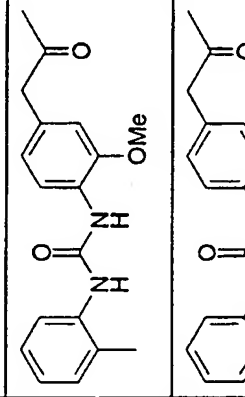
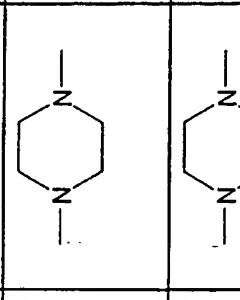
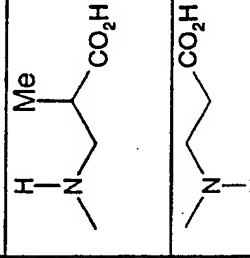
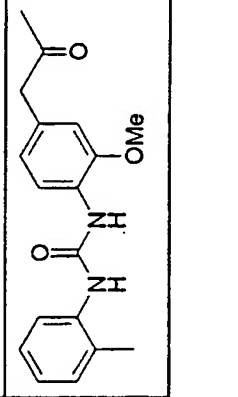
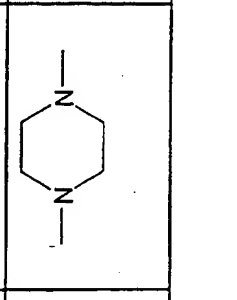
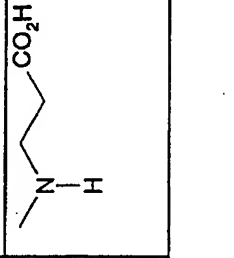
| Compound GK |  |  |  | C26H32N6O7 | 2.78 | 541 |
| Compound GL |  |  |  | C26H32N6O7 | 2.8 | 541 |
| Compound GM |  |  |  | C26H31N5O8 | 2.88 | 542 |
| Compound GN |  |  |  | C26H33N5O6 | 2.99 | 512 |
| Compound GO |  |  |  | C25H31N5O6 | 2.91 | 498 |

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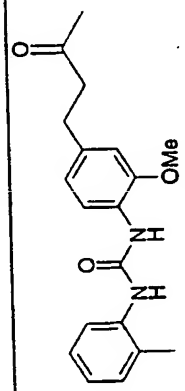
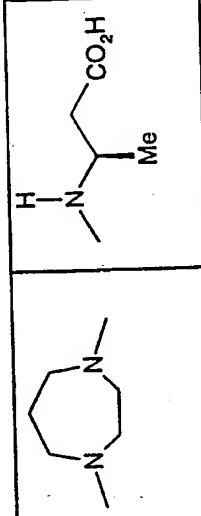
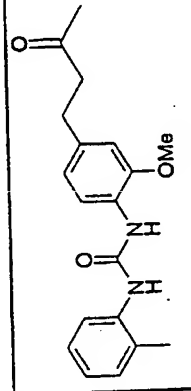
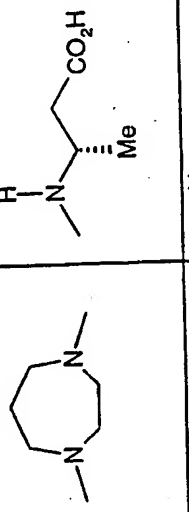
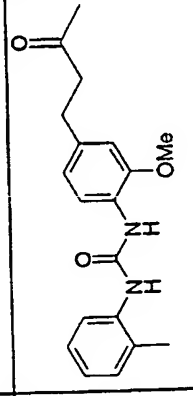
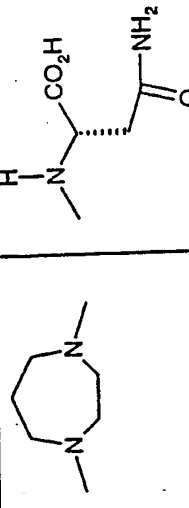
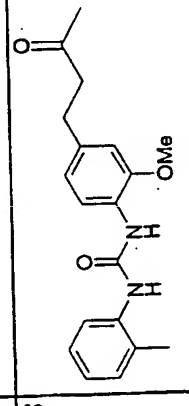
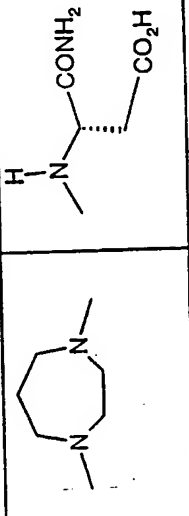
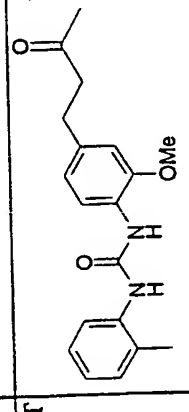
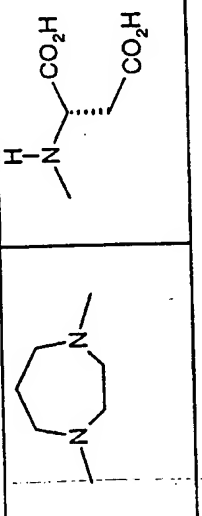
| Compound GP |  |  | C28H37N5O6 | 3.1 | 540 |
| Compound GQ |  |  | C28H37N5O6 | 3.1 | 540 |
| Compound GR |  |  | C28H36N6O7 | 2.88 | 569 |
| Compound GS |  |  | C28H36N6O7 | 2.89 | 569 |
| Compound GT |  |  | C28H35N5O8 | 2.97 | 570 |

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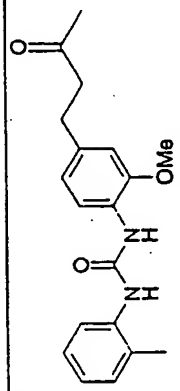
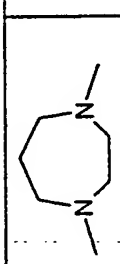
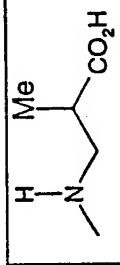
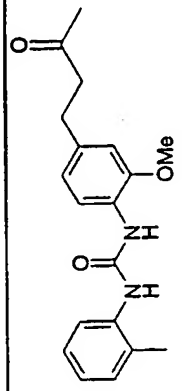
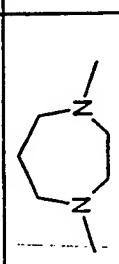
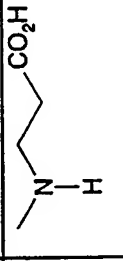
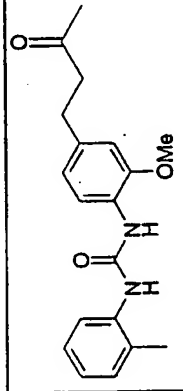
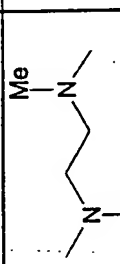
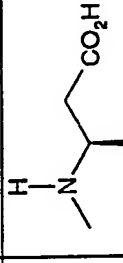
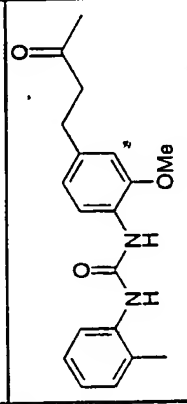
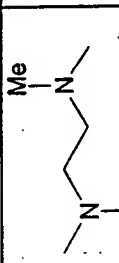
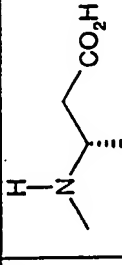
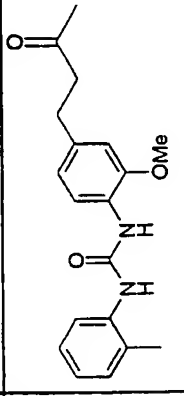
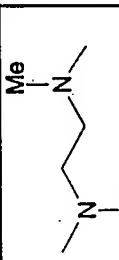
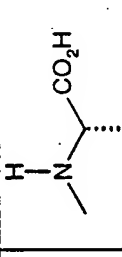
| Compound GU |  |  |  | C28H37N5O6 | 3.09 | 540 |
| Compound GV |  |  |  | C27H35N5O6 | 3.01 | 526 |
| Compound GW |  |  |  | C27H37N5O6 | 3.12 | 528 |
| Compound GX |  |  |  | C27H37N5O6 | 3.11 | 528 |
| Compound GY |  |  |  | C27H36N6O7 | 2.88 | 557 |

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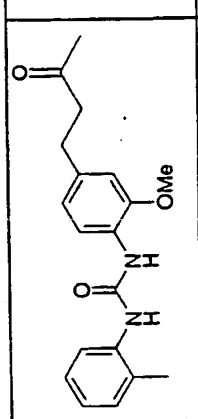
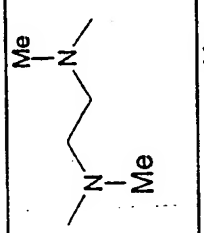
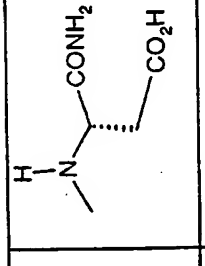
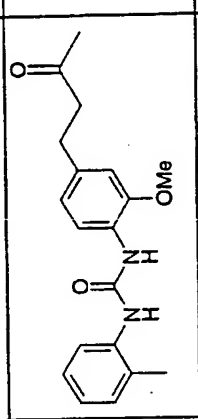
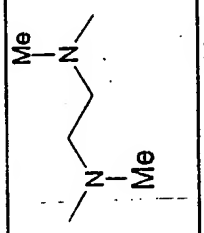
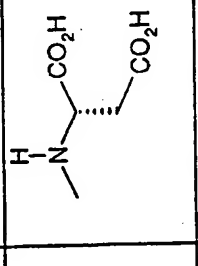
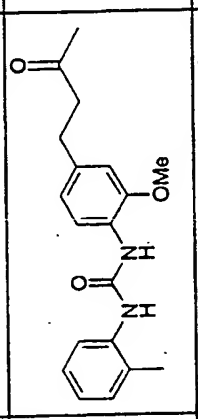
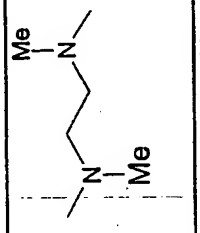
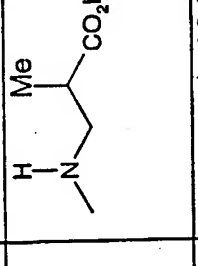
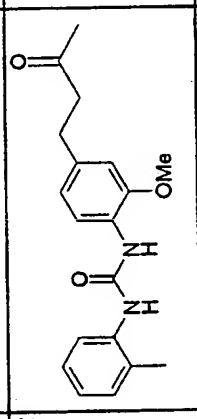
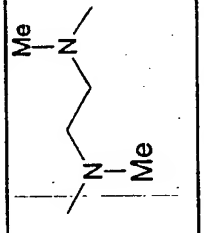
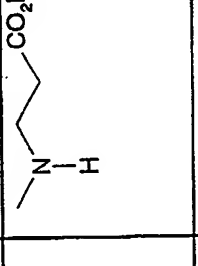
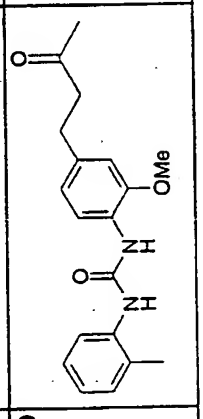
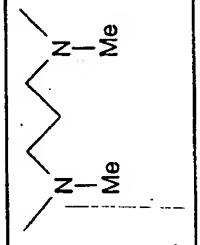
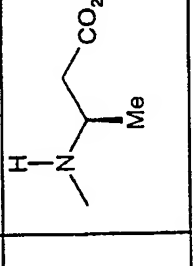
| Compound GZ |  |  |  | C27H36N6O7 | 2.92 | 557 |
| Compound HA |  |  |  | C27H35N5O8 | 2.99 | 558 |
| Compound HB |  |  |  | C27H37N5O6 | 3.12 | 528 |
| Compound HC |  |  |  | C26H35N5O6 | 3.03 | 514 |
| Compound HD |  |  |  | C28H39N5O6 | 3.15 | 542 |

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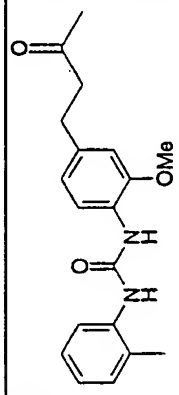
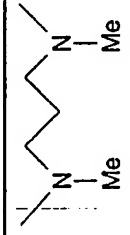
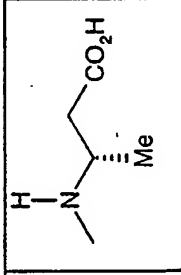
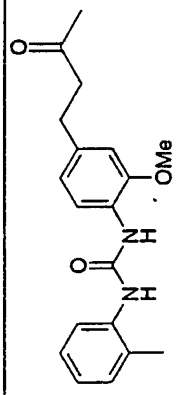
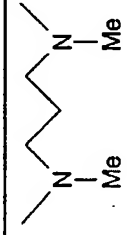
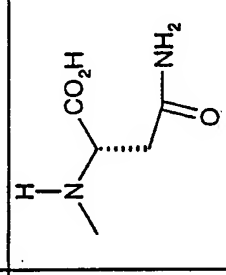
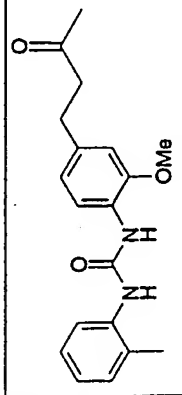
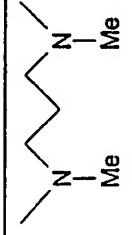
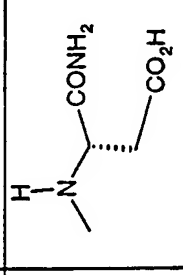
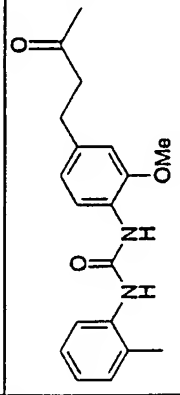
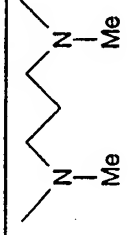
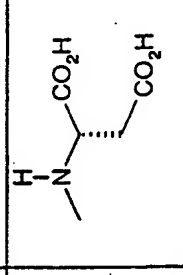
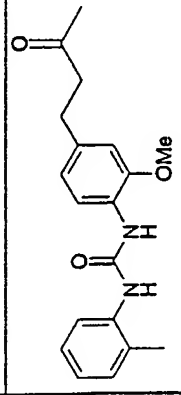
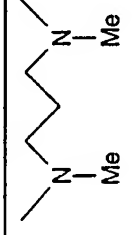
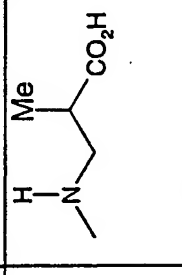
| Compound HE |  |  |  | C28H39N5O6 | 3.15 | 542 |
| Compound HF |  |  |  | C28H38N6O7 | 2.94 | 571 |
| Compound HG |  |  |  | C28H38N6O7 | 2.95 | 571 |
| Compound HH |  |  |  | C28H37N5O8 | 3.03 | 572 |
| Compound HI |  |  |  | C28H39N5O6 | 3.15 | 542 |

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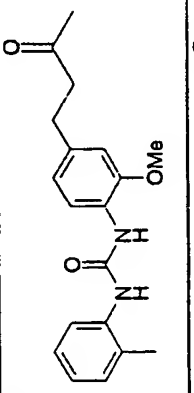
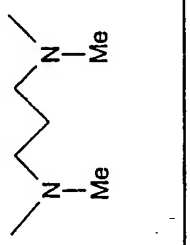
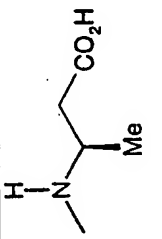
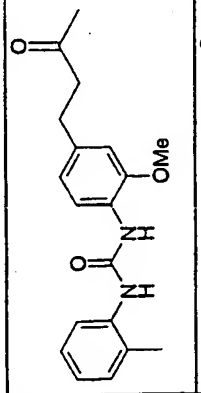
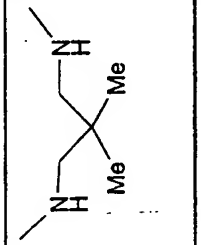
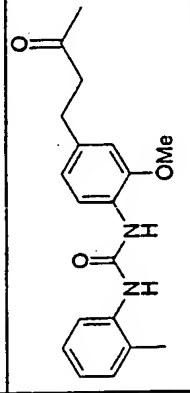
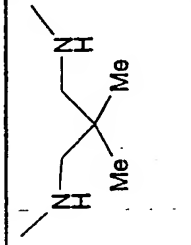
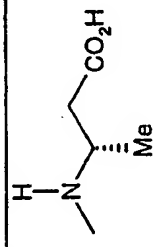
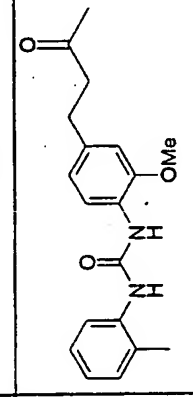
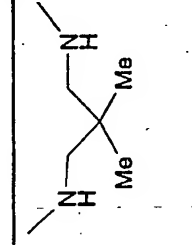
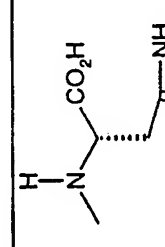
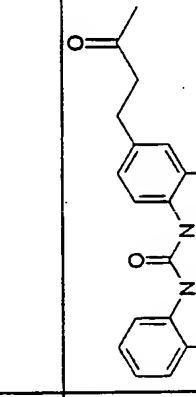
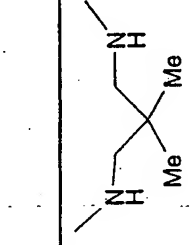
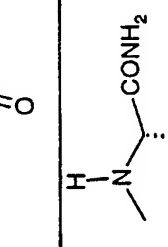
| Compound HJ |  |  |  | C27H37N5O6 | 3.06 | 528 |
| Compound HK |  |  |  | C28H39N5O6 | 3.19 | 542 |
| Compound HL |  |  |  | C28H39N5O6 | 3.19 | 542 |
| Compound HM |  |  |  | C28H38N6O7 | 2.95 | 571 |
| Compound HN |  |  |  | C28H38N6O7 | 2.97 | 571 |

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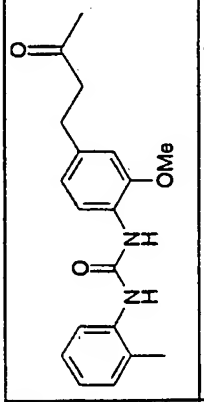
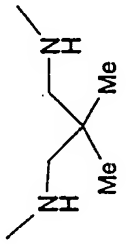
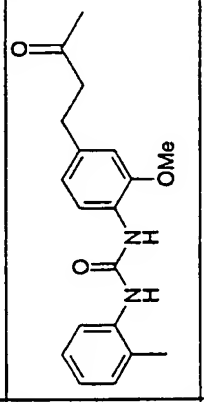
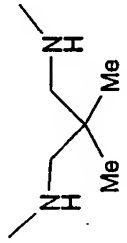
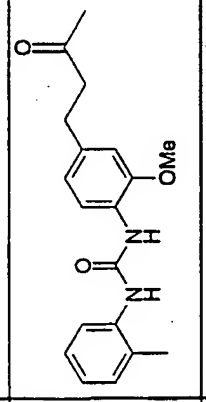
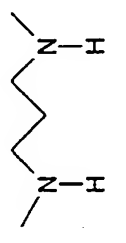
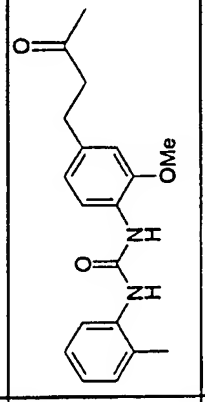
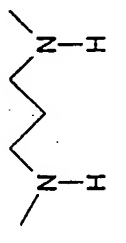
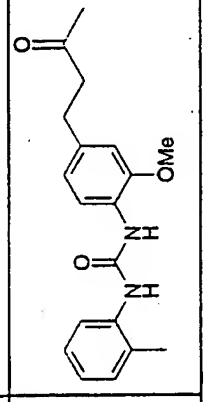
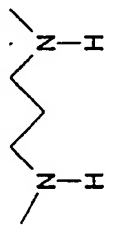
| Compound HO |  |  | C28H39N5O6 | 3.19 | 542 |
| Compound HP |  |  | C27H37N5O6 | 3.1 | 528 |
| Compound HQ |  |  | C26H35N5O6 | 3.01 | 514 |
| Compound HR |  |  | C26H35N5O6 | 2.99 | 514 |
| Compound HS |  |  | C26H34N6O7 | 2.81 | 543 |

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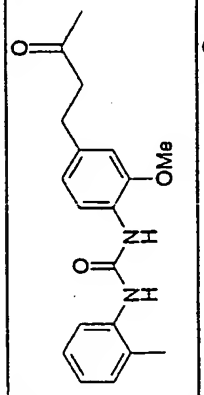
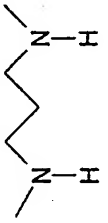
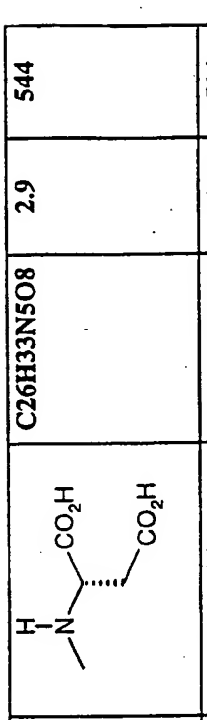
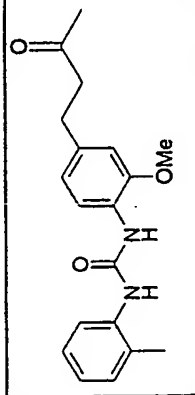
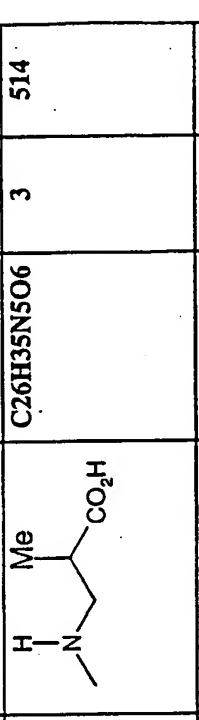
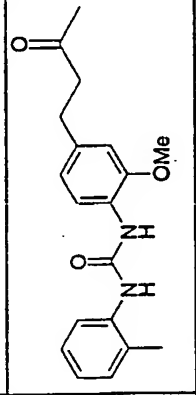
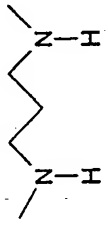
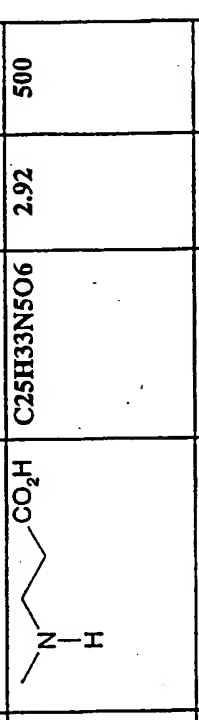
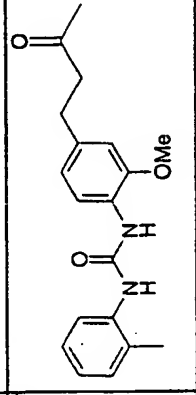
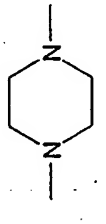
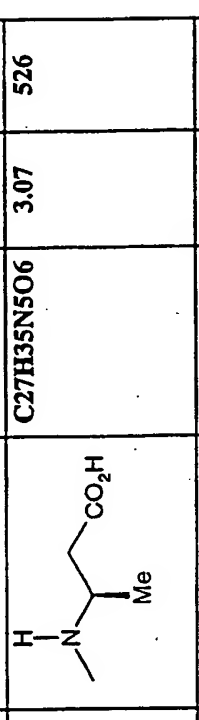
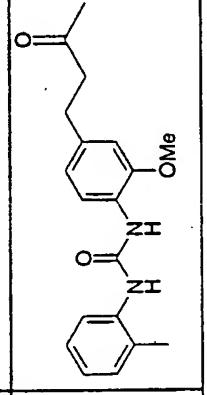
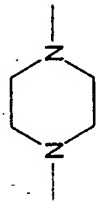
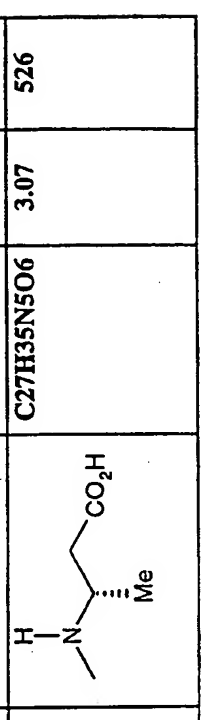
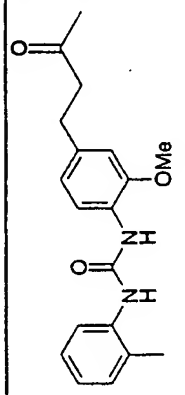
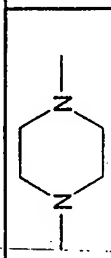
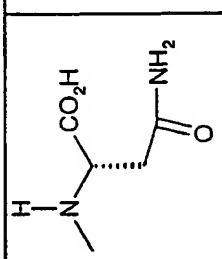
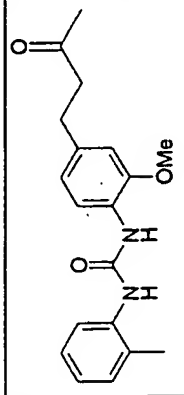
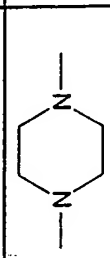
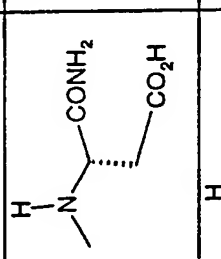
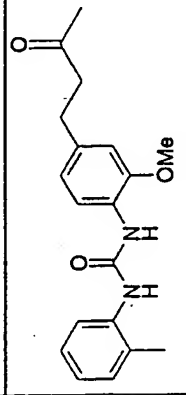
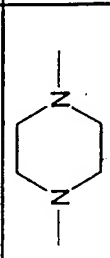
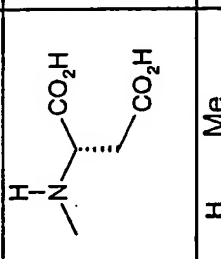
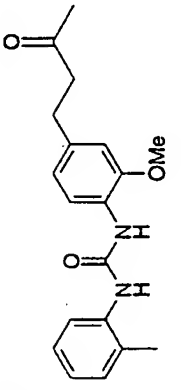
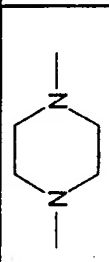
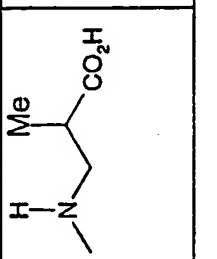
|---|---|---|---|---|---|
| Compound HT |  |  |  | C26H33N5O8 | 544 |
| Compound HU |  |  |  | C26H35N5O6 | 514 |
| Compound HV |  |  |  | C25H33N5O6 | 500 |
| Compound HW |  |  |  | C27H35N5O6 | 526 |
| Compound HX |  |  |  | C27H35N5O6 | 526 |

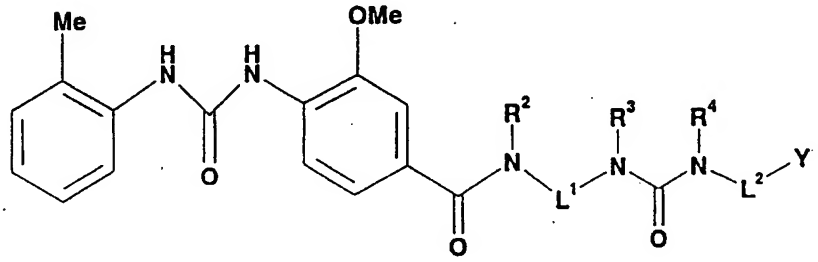
| | | | | | |
|---|---|---|---|---|---|
| Compound HY |  |  |  | C27H34N6O7 | 2.85 | 555 |
| Compound HZ |  |  |  | C27H34N6O7 | 2.87 | 555 |
| Compound IA |  |  |  | C27H33N5O8 | 2.95 | 556 |
| Compound IB |  |  |  | C27H35N5O6 | 3.07 | 526 |

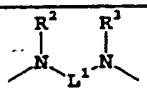
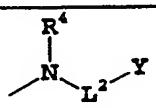
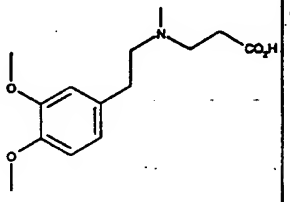
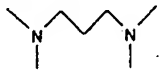
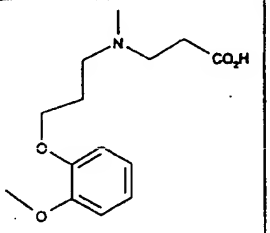
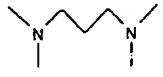
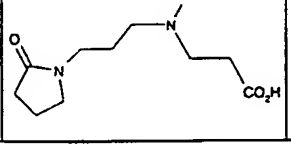
## EXAMPLE 5

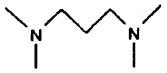
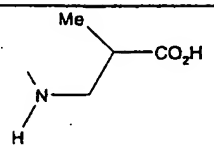
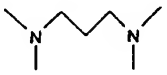
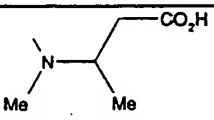
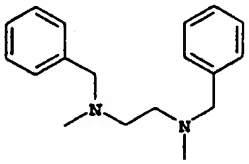
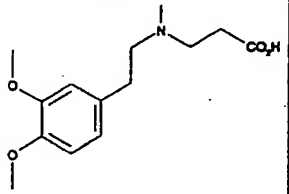
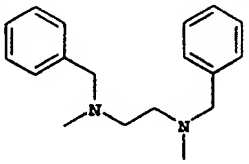
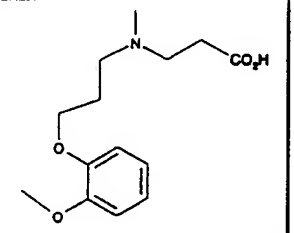
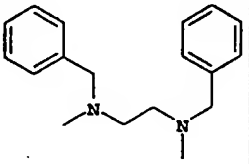
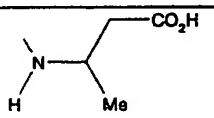
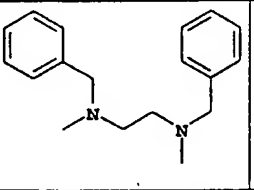
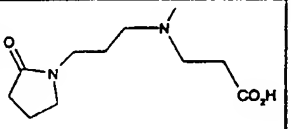
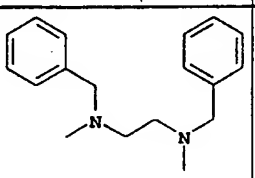
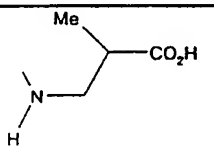
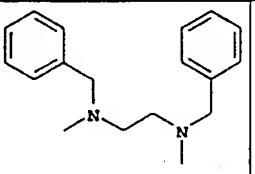
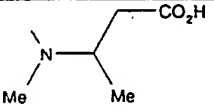
Compounds IC to JH

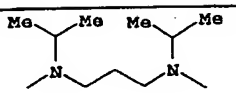
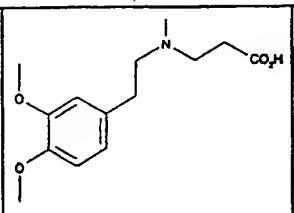
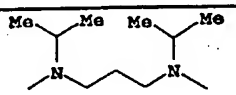
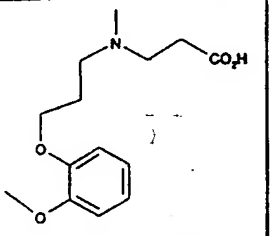
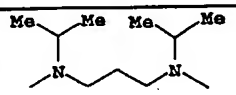
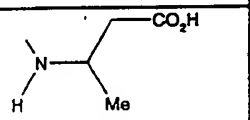
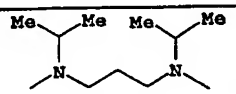
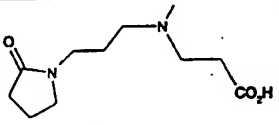
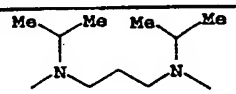
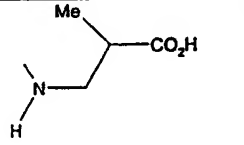
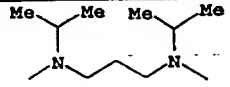
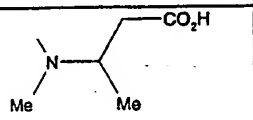
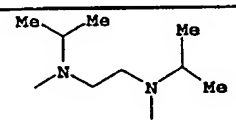
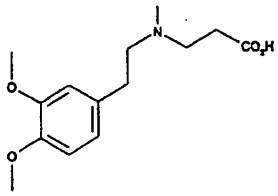
By proceeding in a manner similar to Example 1 (steps 1 and 2), Example 4 (steps 1 to 3) and Example 3 (steps 3 to 5), but using the appropriate diamines in Example 3, step3 and the appropriate acid in Example 3, step 4 , there were prepared the compounds depicted in table 7.

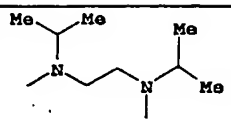
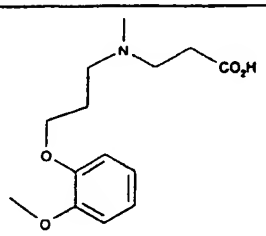
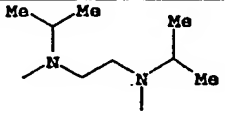
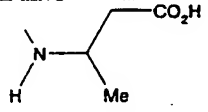
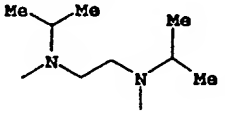
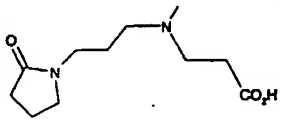
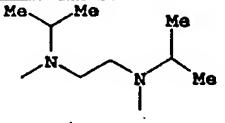
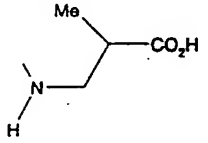
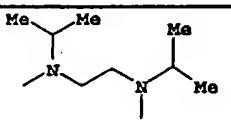
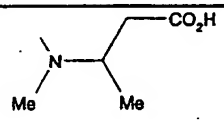
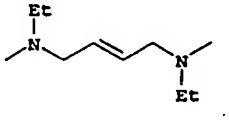
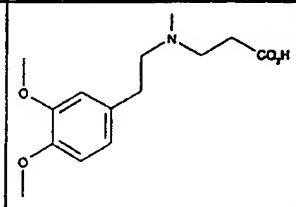
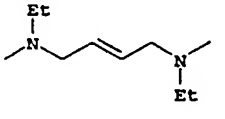
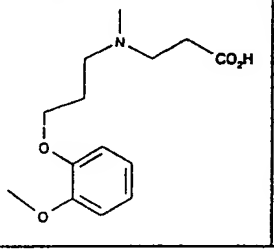
TABLE 7

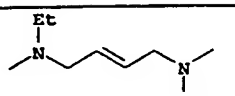
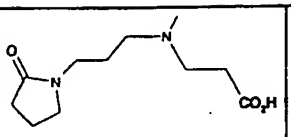
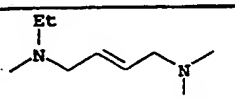
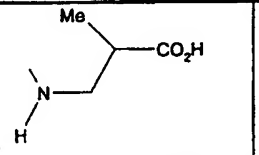
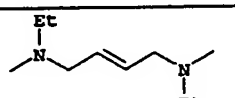
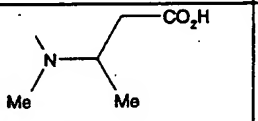
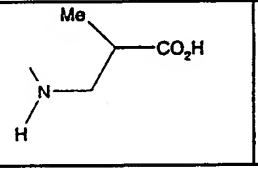



| Compound Number |  |  | Molecular formula | HPLC $R_T$ (minutes) | MS |
|---|---|---|---|---|---|
| Compound IC |  |  | C36H47N5O8 | 3.45 | 678, $M(+H)^+$ |
| Compound ID |  |  | C36H47N5O8 | 3.59 | 678, $M(+H)^+$ |
| Compound IE |  |  | C33H46N6O7 | 3.08 | 639, $M(+H)^+$ |

| | | | | | |
|---|---|---|---|---|---|
| Compound IF |  |  | C27H37N5O6 | 3.1 | 528, $M(+H)^+$ |
| Compound IG |  |  | C28H39N5O6 | 3.23 | 542, $M(+H)^+$ |
| Compound IH |  |  | C47H53N5O8 | 4.17 | 409, $M(+2H)^{2+}$ |
| Compound IJ |  |  | C47H53N5O8 | 4.31 | 409, $M(+2H)^{2+}$ |
| Compound IK |  |  | C38H43N5O6 | 3.98 | 666, $M(+H)^+$ |
| Compound IL |  |  | C44H52N6O7 | 3.78 | 389, $M(+2H)^{2+}$ |
| Compound IM |  |  | C38H43N5O6 | 3.96 | 666, $M(+H)^+$ |
| Compound IN |  |  | C39H45N5O6 | 4.06 | 680, $M(+H)^+$ |

| | | | | | |
|---|---|---|---|---|---|
| Compound IO |  |  | C40H55N5O8 | 3.83 | 368, $M(+2H)^{2+}$ |
| Compound IP |  |  | C40H55N5O8 | 3.98 | 368, $M(+2H)^{2+}$ |
| Compound IQ |  |  | C31H45N5O6 | 3.55 | 584, $M(+H)^{+}$ |
| Compound IR |  |  | C37H54N6O7 | 3.41 | 695, $M(+H)^{+}$ |
| Compound IS |  |  | C31H45N5O6 | 3.56 | 584, $M(+H)^{+}$ |
| Compound IT |  |  | C32H47N5O6 | 3.65 | 598, $M(+H)^{+}$ |
| Compound IU |  |  | C39H53N5O8 | 3.76 | 361, $M(+2H)^{2+}$ |

| | | | | | |
|---|---|---|---|---|---|
| Compound IW |  |  | C39H53N5O8 | 3.93 | 361, M(+2H)$^{2+}$ |
| Compound IY |  |  | C30H43N5O6 | 3.67 | 570, M(+H)$^{+}$ |
| Compound IZ |  |  | C36H52N6O7 | 3.35 | 681, M(+H)$^{+}$ |
| Compound JA |  |  | C30H43N5O6 | 3.67 | 570, M(+H)$^{+}$ |
| Compound JB |  |  | C31H45N5O6 | 3.62 | 584, M(+H)$^{+}$ |
| Compound JC |  |  | C39H51N5O8 | 3.68 | 360, M(+2H)$^{2+}$ |
| Compound JD |  |  | C39H51N5O8 | 3.85 | 360, M(+2H)$^{2+}$ |

| | | | | | |
|---|---|---|---|---|---|
| Compound JE |  |  | C36H50N6O7 | 3.29 | 679, M(+H)$^+$ |
| Compound JF |  |  | C30H41N5O6 | 3.36 | 568, M(+H)$^+$ |
| Compound JG |  |  | C31H43N5O6 | 3.49 | 582, M(+H)$^+$ |
| Compound JH |  |  | C30H39N5O6 | 3.39 | 566, M(+H)$^+$ |

## EXAMPLE 6

Compounds JI to KI , LJ and LK

Step 1. Wang resin (25g, loading 0.9m.mol/g) was swelled with dichloromethane (300mL), drained and resuspended in dichloromethane (50mL). Pyridine (32.7mL) was added followed by the slow addition of a solution of 4-nitrophenyl chloroformate(27g) in dichloromethane (100mL). The mixture was shaken at room temperature for 24hours, then filtered. The modified resin was washed four times with dichloromethane, then 6 times with dimethylformamide, then four times with tetrahydrofuran, then four times with dichloromethane, then three times with diethyl ether and then dried in vacuo.

Step 2. A solution of 4-aminomethylpiperidine (5g) and 3,4-dimethoxybenzaldehyde (7.28g) in dry toluene (87mL) was refluxed under a nitrogen atmosphere whilst removing excluded water with a Dean and Stark apparatus. After 3.5 hours the mixture was cooled to room temperature and concentrated in vacuo to yield 4-(3,4-dimethoxy-phenyliminomethyl)piperidine as a yellow oil. The resin from the foregoing step (14.6g) was swelled with dimethylformamide (100mL) for 10minutes, then drained, then treated with a solution yield 4-(3,4-dimethoxyphenyliminomethyl)piperidine (11.49g) in dimethylformamide (100mL). The mixture was shaken for 20 hours then filtered. The modified resin was washed six times with

dimethylformamide, then four times with tetrahydrofuran, then six times alternatively with methanol then dichloromethane, then four times with diethyl ether and then dried in vacuo.

Step 3. The resin from the foregoing step was treated with a mixture of acetonitrile, water and trifluoroacetic acid (40:10:1, v/v/v, 300mL) and shaken for 2 hours. The resin was filtered, then washed four times with acetonitrile, then four times with dimethylformamide, then three times with a 5% v/v solution of diisopropylethylamine in dimethylformamide, then four times with dimethylformamide, then four times with tetrahydrofuran, then four times with dichloromethane, then four times with diethyl ether and then dried in vacuo.

Step 4. The resin from the foregoing step (1.02g) was swelled with a mixture of dichloromethane and tetrahydrofuran (1:1 v/v, 15mL) for 10 minutes, then drained and then treated with a solution of 4-nitrophenyl chloroformate (532mg) and diisopropylethylamine (460μL) in a mixture of dichloromethane and tetrahydrofuran (1:1 v/v, 15mL). The mixture was shaken for 1.5 hours then filtered. The modified resin was washed four times with a mixture of dichloromethane and tetrahydrofuran (1:1 v/v), then four times with dichloromethane, then four times with diethyl ether and then dried in vacuo.

Step 5. The resin from the foregoing step (242mg) was treated with a mixture of triethylamine and dimethylformamide (1:24 v/v, 1mL), then treated with 1mL of a solution of ethyl isonipecotate (462μL) in dimethylformamide (10mL). The mixture was heated at 60°C for 2h, shaken at room temperature for 13h, and then heated at 60°C for a further 6h. The resin was filtered, washed six times with dimethylformamide, four times with tetrahydrofuran and six times with dichloromethane.

Step 6. The resin from the foregoing step was treated twice with a mixture of dichloromethane and trifluoroacetic acid (1:1, v/v; 4mL), allowed to stand for 30 minutes and then filtered. The resin was washed with a mixture of dichloromethane and trifluoroacetic acid (1:1, v/v; 2mL). The combined filtrates and washings were evaporated. The residue was treated twice with toluene (4mL) followed by concentration in vacuo and then dissolved in dimethylformamide (1mL). The solution was treated with diisopropylethylamine (63μL), then with 1mL of a solution of 3-methoxy-4-[3-(2-methylphenyl)ureido]phenylacetic acid (566.1mg) in dimethylformamide (30mL) and then with 1mL of a solution of O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (684mg) in dimethylformamide (30mL). The mixture was agitated during 18 hours then evaporated. The residue was partitioned between chloroform

(5mL) and aqueous sodium carbonate solution (2mL, 5%) and shaken for 2 hours. The organic phase was collected, and the aqueous phase extracted with chloroform (1mL). The combined organics were evaporated. The residue was partitioned between chloroform (10mL) and aqueous hydrochloric acid (10mL, 2M). The organic phase was separated and evaporated and the residue was treated with toluene (5mL) then evaporated to dryness to give 1-[(1-{[3-methoxy-4-(3-o-tolyl-ureido)-phenyl]-acetyl}-piperidin-4-ylmethyl)-carbamoyl]-piperidine-4-carboxylic acid, ethyl ester.

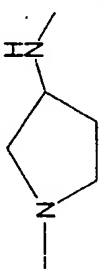
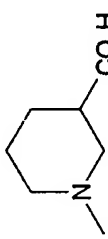
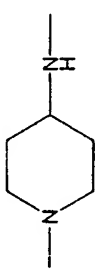
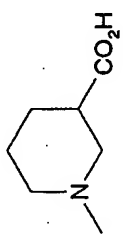
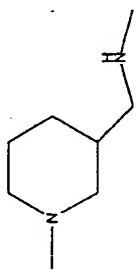
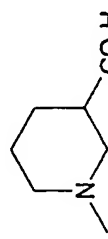
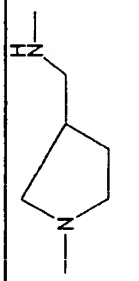
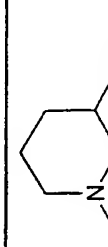
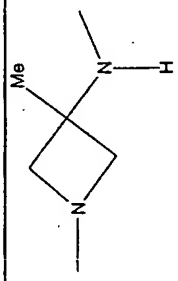
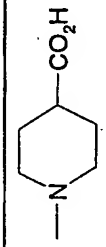
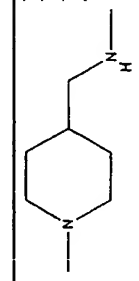
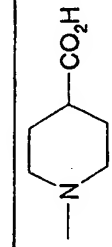
Step7. A solution of 1-[(1-{[3-Methoxy-4-(3-o-tolyl-ureido)-phenyl]-acetyl}-piperidin-4-ylmethyl)-carbamoyl]-piperidine-4-carboxylic acid, ethyl ester from the foregoing step in ethanol (5mL) was treated with a solution of sodium hydroxide (12mg) in water (500µL). After standing at room temperature for 24 hours the mixture was acidified with aqueous hydrochloric acid (2mL,1M) and diluted with water (6mL). The ethanol was evaporated and the remaining aqueous phase was extracted with chloroform (7mL). The chloroform extract was evaporated to give 1-[(1-{[3-methoxy-4-(3-o-tolyl-ureido)-phenyl]-acetyl}-piperidin-4-ylmethyl)-carbamoyl]-piperidine-4-carboxylic acid, Compound JQ.

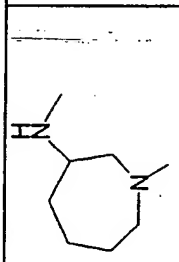
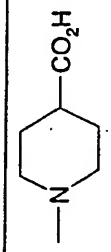
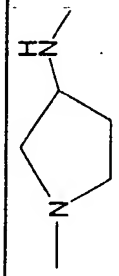
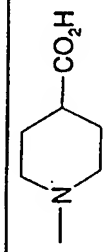
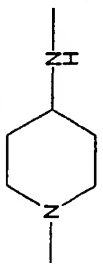
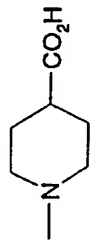
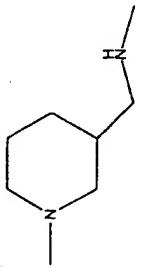
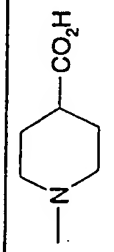
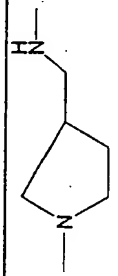
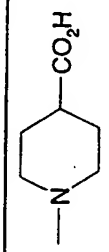
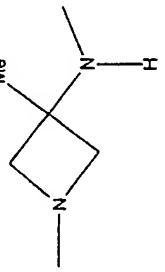
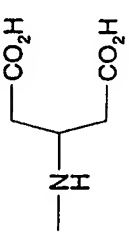
By proceeding in a similar manner to example 6 but using the appropriate diamines in step2 and the appropriate amino ester in step 5 the compounds JI to KI, LJ and LK depicted in table 8 were prepared.

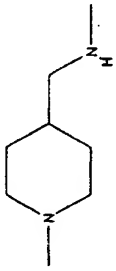
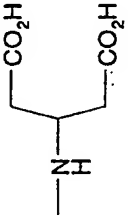
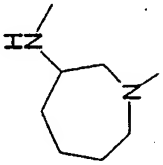
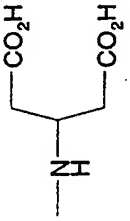
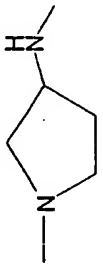
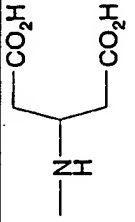
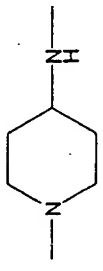
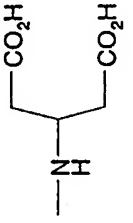
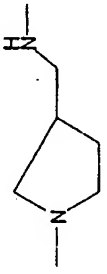
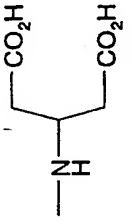
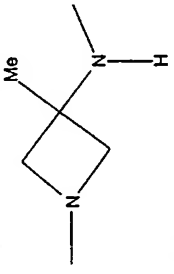
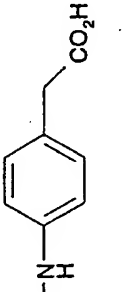
TABLE 8

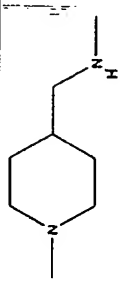
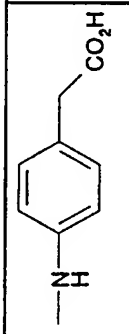
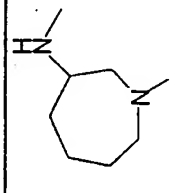
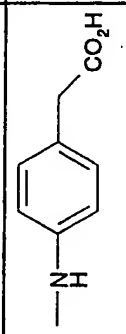
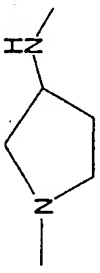
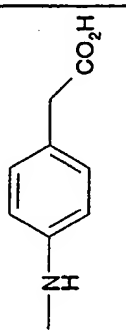
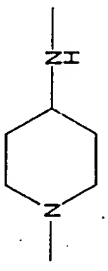
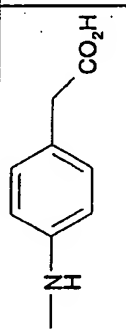
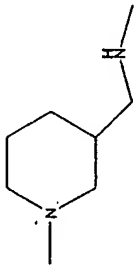
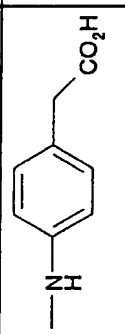
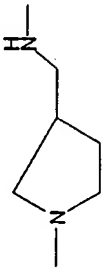
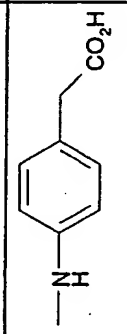


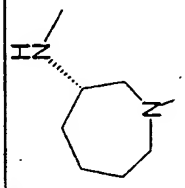
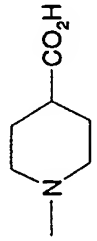
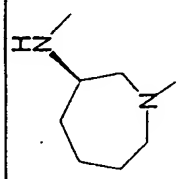
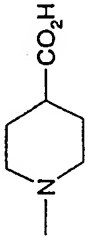
| Compound Number | | | Molecular formula | HPLC $R_T$ (minutes) | MS $(M+H)^+$ |
|---|---|---|---|---|---|
| Compound JI |  |  | C28H35N5O6 | 2.87 | 538 |
| Compound JJ |  |  | C30H39N5O6 | 3.16 | 566 |
| Compound JK |  |  | C30H39N5O6 | 3.35 | 566 |

| | | | | | |
|---|---|---|---|---|---|
| Compound JL |  |  | C28H35N5O6 | 3.09 | 538 |
| Compound JM |  |  | C29H37N5O6 | 3.13 | 552 |
| Compound JN |  |  | C30H39N5O6 | 3.23 | 566 |
| Compound JO |  |  | C29H37N5O6 | 3.11 | 552 |
| Compound JP |  |  | C28H35N5O6 | 2.82 | 538 |
| Compound JQ |  |  | C30H39N5O6 | 3.1 | 566 |

| | | | | | |
|---|---|---|---|---|---|
| Compound JR |  |  | C30H39N5O6 | 3.29 | 566 |
| Compound JS |  |  | C28H35N5O6 | 3.03 | 538 |
| Compound JT |  |  | C29H37N5O6 | 3.08 | 552 |
| Compound JU |  |  | C30H39N5O6 | 3.14 | 566 |
| Compound JV |  |  | C29H37N5O6 | 3.04 | 552 |
| Compound JW |  |  | C27H33N5O8 | 2.94 | 556 |

| | | | | | |
|---|---|---|---|---|---|
| Compound JX |  |  | C29H37N5O8 | 2.97 | 584 |
| Compound JY |  |  | C29H37N5O8 | 3.13 | 584 |
| Compound JZ |  |  | C27H33N5O8 | 2.9 | 556 |
| Compound KA |  |  | C28H35N5O8 | 2.93 | 570 |
| Compound KB |  |  | C28H35N5O8 | 2.95 | 570 |
| Compound KC |  |  | C30H33N5O6 | 3.26 | 560 |

| | | | | | |
|---|---|---|---|---|---|
| Compound KD |  |  | C32H37N5O6 | 3.27 | 588 |
| Compound KE |  |  | C32H37N5O6 | 3.49 | 588 |
| Compound KF |  |  | C30H33N5O6 | 3.18 | 560 |
| Compound KG |  |  | C31H35N5O6 | 3.26 | 574 |
| Compound KH |  |  | C32H37N5O6 | 3.34 | 588 |
| Compound KI |  |  | C31H35N5O6 | 3.23 | 574 |

| | | | | |
|---|---|---|---|---|
| Compound LJ |  |  | C30H39N5O6 | 9.95 | 566 564[(M-H)+] |
| Compound LK |  |  | C30H39N5O6 | 9.97 | 566 564[(M-H)+] |

## EXAMPLE 7

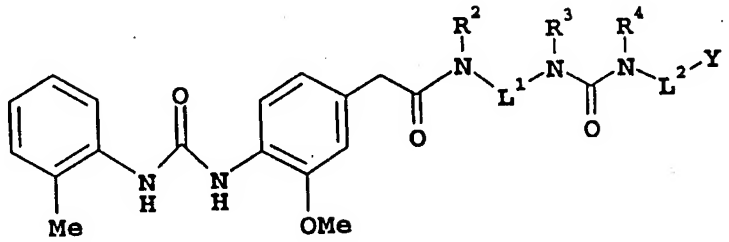
Compounds KJ to KS

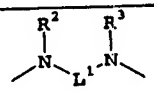
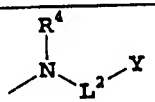
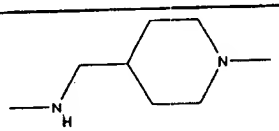
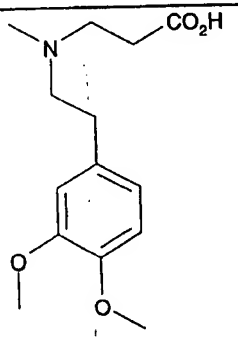
Step 1. The resin from Example 6, Step 2 (3.04g) was swelled with dimethylformamide (50mL) for 10 minutes then drained, then resuspended in dimethylformamide (20mL) and then treated with diisopropylethylamine (0.732mL), then with a solution of 3-methoxy-4-[3-(2-methylphenyl)ureido]phenylacetic acid (440mg) in dimethylformamide(4mL) and then with a solution of O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (532mg) in dimethylformamide. The mixture shaken for 24 hours then filtered. The modified resin was washed six times with dimethylformamide, then six times with dichloromethane, then twice with methanol and then six times with dichloromethane. A mixture of dichloromethane and trifluoroacetic acid (1:1, v/v; 35mL) was added to the resin and the mixture was shaken for 1 hour then filtered. The resin was washed with a mixture of dichloromethane and trifluoroacetic acid (1:1, v/v; 35mL). The combined filtrate and washings were evaporated in vacuo and the residue was used in Step 2 without further purification .

Step 2. Wang resin loaded with N-chloroformyl-N-(2-(3,4-dimethoxyphenyl)ethyl)-Beta-alanine (120mg; loading: 0.5 m.mol/g, prepared by the method described in Example 3, steps 1 to 3) was treated with 1mL of a solution of triethylamine (2.28mL) in dimethylformamide (13mL) then with a solution of the product (69mg) from step 1 in dimethylformamide (2mL). The mixture was shaken for 2 hours then allowed to stand for 16 hours. The resin was drained, then washed six times with dimethylformamide and then six times with dichloromethane. The resin was then treated with a mixture of dichloromethane and trifluoroacetic acid (1:1 v/v, 4mL). After standing for 40 minutes the mixture was filtered. The treatment with dichloromethane and trifluoroacetic acid was repeated. The combined filtrates were evaporated to yield 3-{[2-(3,4-dimethoxy-phenyl)-ethyl]-[4-({2-[3-methoxy-4-(3-o-tolyl-ureido)-phenyl]-acetylamino}-methyl)-piperidine-1-carbonyl]-amino}-propionic acid, Compound KJ.

By proceeding in a similar manner to example 7, but using the appropriately loaded resins in steps 1 and 2, the compounds depicted in table 9 were prepared.

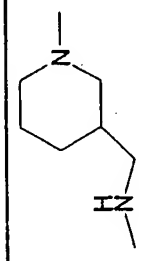
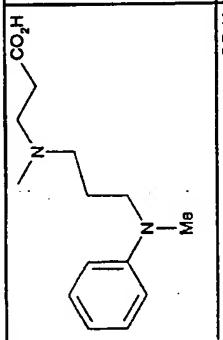
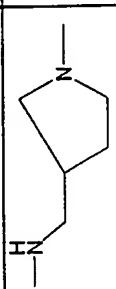
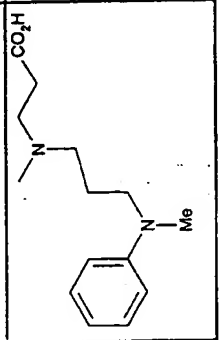
**TABLE 9**




| Compound Number |  |  | Molecular formula | HPLC $R_T$ (minutes) | MS $(M+H)^+$ |
|---|---|---|---|---|---|
| Compound KJ |  |  | C37H47N5O8 | 3.39 | 690 |

| | | | | | |
|---|---|---|---|---|---|
| Compound KK |  |  | C35H43N5O8 | 3.33 | 662 |
| Compound KL |  |  | C36H45N5O8 | 3.58 | 676 |
| Compound KM |  |  | C37H47N5O8 | 3.45 | 690 |

| | | | | | |
|---|---|---|---|---|---|
| Compound KN |  | C36H45N5O8 | 3.36 | 676 | |
| Compound KO |  | C37H48N6O6 | 3.01 | 673 | |
| Compound KP |  | C35H44N6O6 | 2.97 | 645 | |
| Compound KQ |  | C36H46N6O6 | 2.98 | 659 | |

| | | | | | |
|---|---|---|---|---|---|
| Compound KR |  |  | C37H48N6O6 | 3.04 | 673 |
| Compound KS |  |  | C36H46N6O6 | 2.98 | 659 |

## EXAMPLE 8

Compounds KT, KU and KV

Step 1. Bromo-Wang resin (20g, prepared according to the procedure described by K.Ngu and D.V.Patel, Tetrahedron Letters, 1997, 38, page 973) was shaken with Fmoc-b-Ala-OH (8.4g), cesium iodide (4.7g) and dimethylformamide(160ml) for 16 hours. The resin was drained, then and washed six times with dimethylformamide, then three times with methanol, then three times with tetrahydrofuran , then three times with dichloromethane, then three times with diethyl ether and then dried under vacuum.

Step 2. The resin (3g) from Step 1 was treated with 20% piperidine in dimethylformamide and after five minutes was treated with fresh 20% piperidine in dimethylformamide, then washed with dimethylformamide six times, then washed three times with dichloromethane.

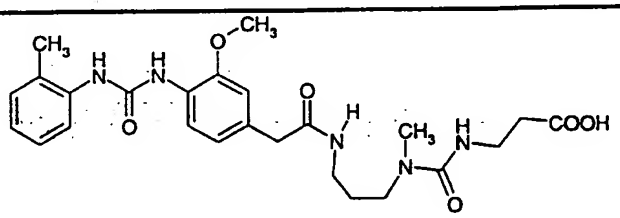
Step 3. A suspension of the resin from Step 2 in dichloromethane (40ml) was treated with diisopropylethylamine (4.83ml) and then with a solution of phosgene in toluene (9ml, 1.93M). After shaking for 1.5 hours the resin was drained, then washed three times with dichloromethane then treated with a solution of 3,4-dimethoxy-3-(N-methyl-3-aminopropylimino)-benzene (4.1g) in a mixture of dimethylformamide (40ml) and triethylamine (5ml). The mixture was shaken for 16 hours then the resin was drained. The resin was washed six times with dimethylformamide, then three times with methanol, then three times with dichloromethane and then three times with acetonitrile.

Step 4. The resin from Step 3 was treated with a solution of acetonitrile (80ml), water (20ml) and trifluoroacetic acid (2ml) and the mixture was shaken for 2 hours. The resin was drained and washed six times with acetonitrile, then three times with methanol, then three times with dichloromethane and then three times with dimethylformamide.

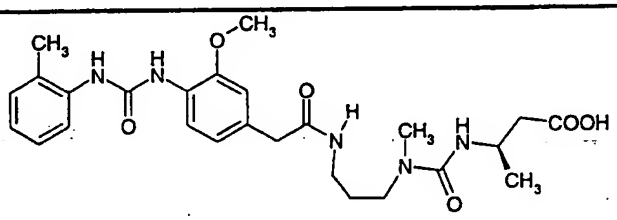
Step 5. The resin (1g) from Step 4 was treated with dimethylformamide (10ml), diisopropylethylamine (1.65ml) , 3-methoxy-4-(3-o-tolyl-ureido)-phenylacetic acid (1.24g) and O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (1.19g). After shaking for 3 hours the resin was drained and then washed six times with dimethylformamide, then three times with methanol, then with tetrahydrofuran , then with dichloromethane, then three times with diethyl ether and then dried under vacuum.

Step 6. The resin from Step 5 was treated with a mixture of trifluoroacetic acid (5ml), dichloromethane (5ml) and water (0.5ml). After one hour the mixture was filtered and the

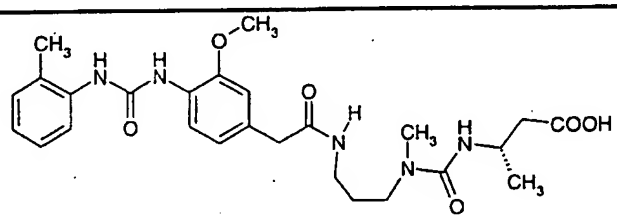
filtrate was evaporated under nitrogen to give a brown oil which was subjected to preparative HPLC (method D) to give the 3-[3-(3-{2-[3-methoxy-4-(3-o-tolyl-ureido)-phenyl]-acetylamino}-propyl)-3-methyl-ureido]-propionic acid (200mg, Compound KT) as a glassy solid. HPLC: $R_T$ (Method C) = 8.0 minutes. MS (MS(ES)): M(-H)$^-$ 498.

| | |
|---|---|
| Compound KT |  |

By proceeding in a similar manner but using Fmoc-(R)-3-aminobutyric acid to replace the Fmoc-β-Ala-OH in Step 1 there was prepared (R)-3-[3-(3-{2-[3-methoxy-4-(3-o-tolyl-ureido)-phenyl]-acetylamino}-propyl)-3-methyl-ureido]-butyric acid (Compound KU). HPLC(Method C): $R_T$=7.4 minutes. MS (ES) : 512 [(M-H)$^-$].

| | |
|---|---|
| Compound KU |  |

By proceeding in a similar manner but using Fmoc-(S)-3-aminobutyric acid to replace the Fmoc-β-Ala-OH in Step 1 there was prepared (S)-3-[3-(3-{2-[3-methoxy-4-(3-o-tolyl-ureido)-phenyl]-acetylamino}-propyl)-3-methyl-ureido]-butyric acid (Compound KV). HPLC(Method C): retention time=7.5 minutes. MS(ES) : 512 [(M-H)$^-$].

| | |
|---|---|
| Compound KV |  |

## EXAMPLE 9

Compounds KW, KX, KY and KZ

Step 1. Wang resin (10g) (Wang S-S, J Am Chem Soc, 1973, 95, page 1328) was shaken with Fmoc-3-aminobutyric acid (9.75g) and 2,6-dichlorobenzoylchoride (4.2ml) in pyridine (4.75g) and dimethylformamide (50ml) for 16 hours. The resin was drained, then washed six times with dimethylformamide, then three times with methanol, then three times with dichloromethane, then three times with diethyl ether and then dried under vacuum.

Step 2. The resin (0.9g) form Step 1 was treated with 20% piperidine in dimethylformamide and after five minutes was treated with fresh 20% piperidine in dimethylformamide, and then washed with dimethylformamide six times, then three times with methanol, then three times with tetrahydrofuran and then with a mixture of dichloromethane and tetrahydrofuran (1:1, v/v).

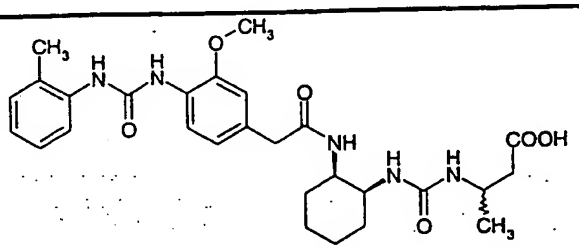
Step 3. The resin from Step 2 was treated with a mixture of p-nitrophenylchloroformate (1.43g) and diisopropylethylamine (1.23ml) in a mixture of dichloromethane and tetrahydrofuran (1:1, v/v, 10ml). After shaking the mixture for one hour the resin was drained then washed three times with a mixture of dichloromethane and tetrahydrofuran (1:1, v/v).

Step 4. The resin from Step 3 was treated with cis-cyclohexyldiamine (0.81g) in dimethylformamide (20ml). After shaking for one hour the resin was drained and then washed six times with dimethylformamide, then three times with tetrahydrofuran, then with a mixture of dichloromethane and tetrahydrofuran (1:1. v/v), then with dichloromethane then with diethyl ether and then dried under vacuum.

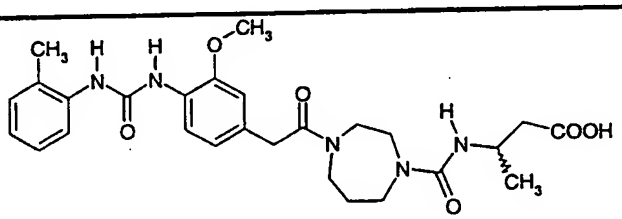
Step 5. The resin (1g) from Step 4 was treated with dimethylformamide (10ml), diisopropylethylamine (1.65ml) , 3-methoxy-4-(3-o-tolyl-ureido)-phenyl-acetic acid (1.24g) and O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (1.19g). After shaking for 3 hours the resin was drained and then washed six times with dimethylformamide, then three times with methanol, then with tetrahydrofuran, then with dichloromethane, then with diethyl ether and then dried under vacuum.

Step 6. The resin from Step 5 was treated with a mixture of trifluoroacetic acid (5ml) , dichloromethane (5ml) and water (0.5ml) for one hour. The mixture was filtered and the filtrate was evaporated under nitrogen to give a brown oil which was subjected to preparative HPLC (method D) to give 3-[3-(2-[2-[3-methoxy-4-(3-o-tolyl-ureido)-phenyl]-acetylamino}-cyclohexyl)-

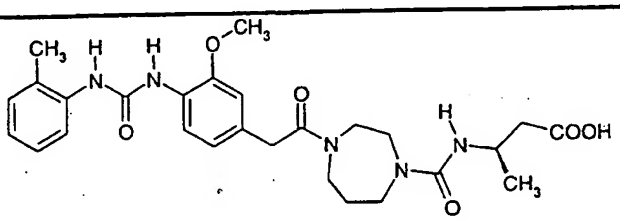
ureido]-butyric acid (200mg, Compound KW) as a glassy solid. LC-MS : 540 (M+H), $R_T$=9.57 minutes. MS(ES) : 538[(M-H)$^-$], 540(M+H).

| | |
|---|---|
| Compound KW |  |

By proceeding in a similar manner but using homopiperidine to replace the cis-cyclohexyldiamine in Step 4 there was prepared 3-[(4-{[3-methoxy-4-(3-o-tolyl-ureido)-phenyl]-acetyl}-[1,4]diazepane-1-carbonyl)-amino]-butyric acid (Compound KX). LC-MS : 526(M+H), $R_T$=9.33 minutes. MS (ES) : 524[(M-H)$^-$].

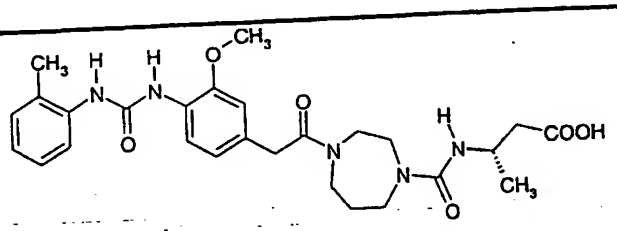
| | |
|---|---|
| Compound KX |  |

By proceeding in a similar manner but using Fmoc-(S)-3-aminobutyric acid to replace the Fmoc-3-aminobutyric acid in Step 1 there was prepared 3-[(4-{[3-methoxy-4-(3-o-tolyl-ureido)-phenyl]-acetyl}-[1,4]diazepane-1-carbonyl)-amino]-butyric acid (Compound KY). HPLC(Method B): $R_T$=7.4 minutes. MS (ES) : 524[(M-H)$^-$].

| | |
|---|---|
| Compound KY |  |

By proceeding in a similar manner but using Fmoc-(R)-3-aminobutyric acid to replace the Fmoc-3-aminobutyric acid in Step 1 there was prepared 3-[(4-{[3-methoxy-4-(3-o-tolyl-ureido)-phenyl]-

acetyl}-[1,4]diazepane-1-carbonyl)-amino]-butyric acid (Compound KZ). HPLC(Method B): $R_T$=7.0 minutes. MS (ES) : 524[(M-H)$^-$].

| | |
|---|---|
| Compound KZ |  |

## EXAMPLE 10

Compounds LA, LB and LC

Step 1. Wang resin loaded with an acrolyl group (10g, prepared as described by A.R.Brown et al, J.Am.Chem.Soc, 1997, 119, page 3288, 1997) was treated with 1-(3-aminopropyl)-2-pyrrolidinone (18.1g) in dimethylformamide (150ml). After 16 hours the resin was then drained then washed six times with dimethylformamide, then three times with methanol, then with tetrahydrofuran , then with dichloromethane then with diethyl ether and then dried under vacuum.

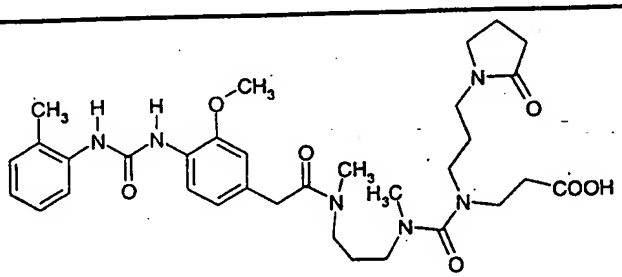
Step 2. Resin (3g) from Step 1 was treated with dichloromethane (50ml) then with diisopropylethylamine (5ml) and after mixing for 2 minutes the mixture was added to a solution of phosgene in toluene (11ml, 1.93M). After shaking for 90 minutes the resin was drained and washed six times with dichloromethane, then twice with dimethylformamide.

Step 3. The resin from Step 2 was treated with dimethylformamide (50ml) and triethylamine (5ml) then with N,N'-dimethylpropylamine (1.84g). After shaking for 2 hours the resin was then drained and then washed with dimethylformamide eight times.

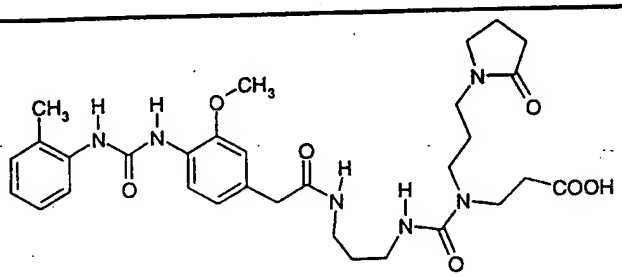
Step 4. The resin from Step 3 was treated with dimethylformamide (50ml), diisopropylethylamine (1.56ml) , 3-methoxy-4-(3-o-tolyl-ureido)-phenylacetic acid (1.13g) and O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (1.37g). After shaking for 12 hours the resin was drained and then washed six times with dimethylformamide, then three times with methanol, then with tetrahydrofuran, then with dichloromethane, then with diethyl ether and then dried under vacuum.

Step 5. The resin from Step 4 was treated with a mixture of trifluoroacetic acid (30ml) and water (3ml). After one hour the mixture was filtered and the filtrate evaporated under nitrogen to give

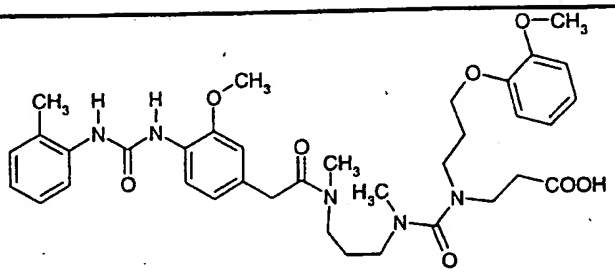
a brown oil which was subjected to preparative HPLC (method D) to give 3-{3-[3-({[3-methoxy-4-(3-o-tolyl-ureido)-phenyl]-acetyl}-methyl-amino)-propyl]-3-methyl-1-[3-(2-oxo-pyrrolidin-1-yl)-propyl]-ureido}-propionic acid (200mg, Compound LA) as a glassy solid. HPLC(Method A) $R_T$=16.1 minutes. MS(ES) : 639(M+H).

| | |
|---|---|
| Compound LA |  |

By proceeding in a similar manner but using 1,3-diaminopropane instead of N,N'-dimethylpropylamine in Step 3 there was prepared 3-{3-(3-{2-[3-methoxy-4-(3-o-tolyl-ureido)-phenyl]-acetylamino}-propyl)-1-[3-(2-oxo-pyrrolidin-1-yl)-propyl]-ureido}-propionic acid (Compound LB). HPLC(Method B): $R_T$=8.95 minutes. MS(ES) : 611(M+H); 609[(M-H)$^-$].

| | |
|---|---|
| Compound LB |  |

By proceeding in a similar manner but using 2-methoxy-phenoxypropylamine (Reference Example 2) instead of 1-(3-aminopropyl)-2-pyrrolidinone there was prepared 3-{1-[3-(2-methoxy-phenoxy)-propyl]-3-[3-({[3-methoxy-4-(3-o-tolyl-ureido)-phenyl]-acetyl}-methyl-amino)-propyl]-3-methyl-ureido}-propionic acid (Compound LC). HPLC(Method C): $R_T$=9.43 minutes. MS(ES) : 677[(M-H)$^-$].

| | |
|---|---|
| Compound LC |  |

## EXAMPLE 11

Compounds LD and LE

Step 1. Bromo-Wang resin (20g, prepared according to the procedure described by K.Ngu and D.V.Patel, Tetrahedron Letters, 1997, 38, page 973) was shaken with Fmoc-3-oxopiperazin-2-yl-acetic acid (5.13g, Reference Example 3), caesium iodide (2.34g) and dimethylformamide(100ml) for 16 hours. The resin was drained, then and washed six times with dimethylformamide, then three times with methanol, then three times with tetrahydrofuran , then three times with dichloromethane, then three times with diethyl ether and then dried under vacuum.

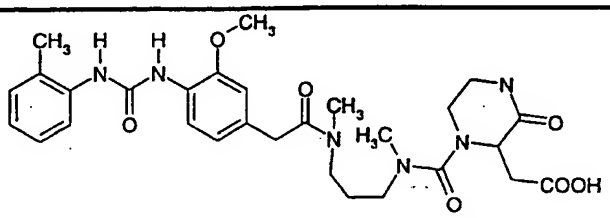
Step 2. The resin (4g) from Step 1 was treated with 20% piperidine in dimethylformamide and after five minutes was treated with fresh 20% piperidine in dimethylformamide, then washed with dimethylformamide six times, then washed three times with dichloromethane.

Step 3. A suspension of the resin from Step 2 in dichloromethane (30ml) was treated with diisopropylethylamine (4.83ml) and then with a solution of phosgene in toluene (7.5ml, 1.93M). After shaking for 1.5 hours the resin was drained, then washed six times with dichloromethane, then twice with dimethylformamide.

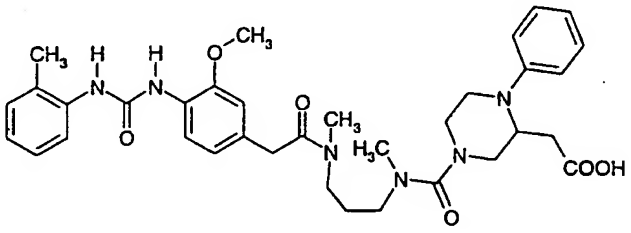
Step 4. The resin from Step 3 was treated with N,N'dimethylpropyldiamine (1.23g) in dimethylformamide(30ml) and triethylamine (3.5mls). After shaking for 2 hours the resin was drained and then washed eight times with dimethylformamide.

Step 5. The resin from Step 4 was treated with dimethylformamide (40ml), diisopropylethylamine (1.3ml), 3-methoxy-4-(3-o-tolyl-ureido)-phenylacetic acid (0.78g) and O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (0.95g). After shaking for 12 hours the resin was drained and then washed six times with dimethylformamide, then three times with methanol, then with dichloromethane, then with diethyl ether and then dried under vacuum.

Step 6. The resin from Step 5 was treated with a mixture of trifluoroacetic acid, dichloromethane, water (35:15:5, 20ml). After one hour the resin was filtered and the filtrate evaporated under nitrogen to give a brown oil which was subjected to preparative HPLC (method D) to give (1-{[3-({[3-methoxy-4-(3-o-tolyl-ureido)-phenyl]-acetyl}-methyl-amino)-propyl]-methyl-carbamoyl}-3-oxo-piperazin-2-yl)-acetic acid (200mg, Compound LD) as a glassy solid. HPLC(Method B): $R_T$=8.99 minutes. MS(ES) : 581[(M-H)$^-$].

| | |
|---|---|
| Compound LD |  |

By proceeding in a similar manner but using Fmoc-4-phenyl-piperazin-2-yl-acetic acid (Reference Example 4) instead of Fmoc-3-oxopiperazin-2-yl-acetic acid there was prepared (1-{[3-({[3-methoxy-4-(3-o-tolyl-ureido)-phenyl]-acetyl}-methyl-amino)-propyl]-methyl-carbamoyl}-4-phenyl-piperazin-2-yl)-acetic acid (Compound LE). HPLC(Method A): $R_T$=16.8 minutes. MS(ES) : 643[(M-H)$^-$].

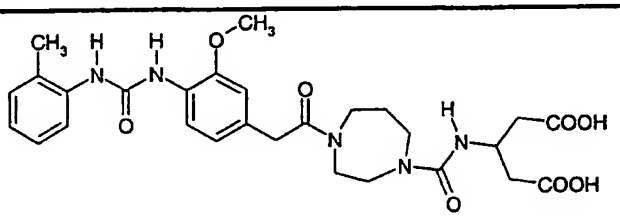
| | |
|---|---|
| Compound LE |  |

## EXAMPLE 12

Compound LF

A mixture of [1,4]diazepane-1-carbonyl)-amino]-pentanedioic acid (150mg, Reference Example 5), chloroform (10ml), diisopropylethylamine (258mg), 3-methoxy-4-(3-o-tolyl-ureido)-phenylacetic acid (157mg) and O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (190mg) was stirred for 2.5 hours and then washed twice with aqueous sodium carbonate solution (10ml, 5%). The organic layer was dried with anhydrous magnesium sulphate then evaporated. The resulting clear oil was treated with methanol (20ml) and sodium hydroxide (1g) in water (10ml). After stirring for 16 hours the mixture was evaporated. The

residue was treated with water (20ml) and the pH of the mixture was adjusted to 2 by addition of hydrochloric acid (1N). The resulting oil was extracted with ethyl acetate. The organics were dried over magnesium sulphate and evaporated to give a clear oil that crystallised on standing. The solid was subjected to preparative HPLC (method D) affording 3-[(4-{[3-methoxy-4-(3-o-tolyl-ureido)-phenyl]-acetyl}-[1,4]diazepane-1-carbonyl)-amino]-pentanedioic acid (100mg, Compound LF). HPLC(Method C): $R_T$=13.95 minutes. MS(ES) : 568[(M-H)$^-$].

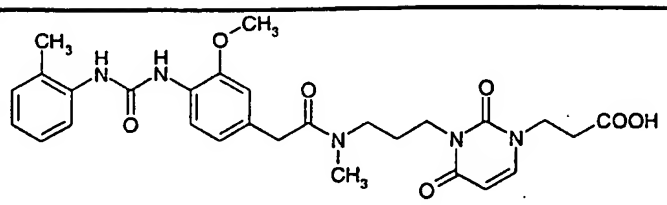
| | |
|---|---|
| Compound LF |  |

## EXAMPLE 13

Compound LI

A mixture of ethyl-3-(2,4-dioxo-3,4-dihydro-2H-pyrimidin-1yl)-propionate (3.18g, Reference Example 6), 1,3-dibromopropane (12g) and potassium carbonate (6.21g) in dry dimethylformamide (30ml) was stirred at 60°C for 1.5hours. The mixture was evaporated and the residue was treated with ethanol (100ml) then with methylamine (38ml, 8M). After stirring at 50°C for 16 hours the mixture was evaporated and the residual clear oil (1g) was treated with dimethylformamide (50ml), diisopropylethylamine (1.1ml), 3-methoxy-4-(3-o-tolyl-ureido)-phenylacetic acid (942mg) and O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (1140mg). After stirring for 2 hours the mixture was evaporated and the resulting oil was taken up in ethyl acetate and then washed twice with 5% aqueous sodium carbonate (50ml). The organic layer was separated, dried over magnesium sulphate then evaporated. The residual yellow oil was stirred with 1N HCl (100ml) and tetrahydrofuran (50ml) for 16 hours. The reaction mixture was evaporated and the product taken up in chloroform, dried over magnesium sulphate and then evaporated to give 3-{3-[3-({[2-methoxy-3-(3-o-tolyl-ureido)-phenyl]-acetyl}-methyl-amino)-propyl]-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl}-propionic acid (Compound LI) as a yellow powder. HPLC(Method B): $R_T$=9.9 minutes.

MS(ES) : 550[M-H)$^-$].

| | |
|---|---|
| Compound LI |  |

## EXAMPLE 14

Compound LL

By proceeding in a similar manner to that described in Example 6 Step 7 but using 1-(4-{[3-methoxy-4-(3-o-tolylureido)phenyl]acetyl}-[1,4]-diazepane-1-carbonyl)piperidine-4-carboxylic acid ethyl ester (Reference Example 8) there was prepared 1-(4-{[3-methoxy-4-(3-o-tolylureido)phenyl]acetyl}-[1,4]-diazepane-1-carbonyl)piperidine-4-carboxylic acid (Compound LL). HPLC: $R_T$=9.45 minutes. MS(ES): 550[(M-H)+]

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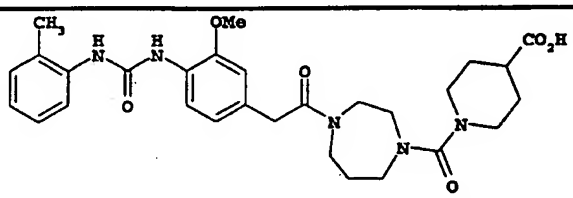
|---|---|
| Compound LL |  |

## EXAMPLE 15

Compound LR

A solution of ethyl-(4-{2-[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylamino}-piperidin-1-yl)-acetate (0.23g, Reference Example 12) in a mixture of methanol and 1M sodium hydroxide (30ml , 2:1, v/v) was heated at reflux temperature for 18 hours. After cooling the reaction mixture was evaporated and the solid residue was treated with water(10ml). The pH of the resulting solution was adjusted to pH 6 by addition of hydrochloric acid (1M). The resulting precipitate was filtered, then washed with water and then dried under vacuum to afford (4-{2-[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylamino}-piperidin-1-yl)-acetic acid (0.15g, Compound LR) as a white solid, m.p. 225°C. MS(Electron Impact): 455($M^+$).

## EXAMPLE 16

Compounds LS and LT

Step 1. A suspension of Wang resin (15g , Advanced ChemTech) in dichloromethane (200ml) was treated with diisopropylethylamine (9ml) then with acryloyl chloride (4.5ml). The mixture was kept at ambient temperature for 3 hours with occasional agitation. The resin was filtered

and then washed three times with 50ml portions each of dichloromethane, tetrahydrofuran, dimethylformamide, tetrahydrofuran and dichloromethane, and then dried under vacuum.

Step 2. The acrylate-loaded Wang resin from Step 1 (0.6g, 0.92mmol/g loading) was treated with a solution of piperazine (0.6g) in dimethylsulphoxide (6ml). The mixture was shaken gently for 18 hours. The resin was drained and then washed twice with dimethylsulphoxide, then three times with dimethylformamide, then three times with tetrahydrofuran, then three times with dichloromethane, then sucked dry and then dried under high vacuum.

Step 3. The resin from step 2 (50mg, nominal 0.046mmol/g loading) was treated successively at room temperature with a solution of 4-[3-(2-methylphenyl)ureido]-phenylacetic acid (0.092mmol, prepared as described in International Patent Application Publication No. WO 96/22966), in dimethylformamide (0.75ml), then with diisopropylethylamine (50µl) and then with a solution of O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (0.092mmol) in dimethylformamide (0.75ml). The mixture was kept at room temperature for 1-2 hours, then the resin drained, and then washed three times with dimethylformamide, then three times with tetrahydrofuran, then three times with dichloromethane, and then dried under high vacuum.

Step 4. The resin from step 3 was treated with a mixture of trifluoroacetic acid and dichloromethane (2 ml , 1:1, v/v). After 1 -2 hours at room temperature the resin was drained and then washed with a mixture of trifluoroacetic acid and dichloromethane (2ml). The combined filtrate and washings were evaporated to give 3-(4-{[4-(3-(2-methylphenyl)ureido)-phenyl]-acetyl}-piperazin-1-yl)-propionic acid (Compound LS). MS: 425($MH^+$). HPLC: $R_T$=10.00 minutes [HPLC column 5 micron Hypersil Elite C18 operated under gradient elution conditions with a mixture of acetonitrile and water plus 0.1% trifluoroacetic acid as the mobile phase (0-3 minutes 20% acetonitrile; 3-14 minutes ramp up to 80% acetonitrile; 15 minutes to end of run 80% acetonitrile) and UV detection at 220nm].

By proceeding in a similar manner but using homopiperazine in step 2, there was prepared 3-(4-{[4-(3-(2-methylphenyl)ureido)-phenyl]-acetyl}-homopiperazin-1-yl)-propionic acid (Compound LT). MS: 439($MH^+$). HPLC:$R_T$=10.08 minutes.

## EXAMPLE 17

Compounds LU, LV and LW

Step 1: A stirred solution of bromoacetic acid (1.28g) in dimethylformamide (10ml) and tetrahydrofuran (5ml) was treated with diisopropyl-carbodiimide (0.59g). After stirring for 5 minutes, the solution was treated with 4-(dimethylamino)pyridine (10mg) and then with Wang resin (1g, Advanced ChemTech). The mixture was allowed to stand at ambient temperature for 18 hours. The resin was drained and then washed three times with dimethylformamide, then three times with tetrahydrofuran, then three times with dichloromethane, then sucked dry and then dried under vacuum.

Step 2. The resin from step 1 with a solution of piperazine (0.6g) in dimethylsulphoxide (6ml). The mixture was shaken gently for 18 hours. The resin was drained and then washed twice with dimethylsulphoxide, three times with dimethylformamide, three times with tetrahydrofuran, three times with dichloromethane, then sucked dry and then dried under high vacuum.

Step 3. The resin from step 2 (50mg, nominal 0.046mmol/g loading) was treated successively at room temperature with a solution of 4-[3-(2-methylphenyl)ureido]-phenylacetic acid (0.092mmol) in dimethylformamide (0.75ml), then with diisopropylethylamine (50µl) and then with a solution of O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (0.092mmol) in dimethylformamide (0.75ml). The mixture was kept at room temperature for 1-2 hours, then the resin drained, and then washed three times with dimethylformamide, three times with tetrahydrofuran, three times with dichloromethane, and dried under high vacuum.

Step 4. The resin from step 3 was treated with a mixture of trifluoroacetic acid and dichloromethane (2 ml , 1:1, v/v). After 1 -2 hours at room temperature the resin was drained and then washed with a mixture of trifluoroacetic acid and dichloromethane (2ml). The combined filtrate and washings were evaporated to give(4-{[4-(3-(2-methylphenyl)ureido)-phenyl]-acetyl}-piperazin-1-yl)-acetic acid (Compound LU). MS: $MH^+$ 411. HPLC retention time=9.95 minutes [HPLC column 5 micron Hypersil Elite C18 operated under gradient elution conditions with a mixture of acetonitrile and water plus 0.1% trifluoroacetic acid as the mobile phase (0-3 minutes 20% acetonitrile; 3-14 minutes ramp up to 80% acetonitrile; 15 minutes to end of run 80% acetonitrile) and UV detection at 220nm].

By proceeding in a similar manner but using homopiperazine in step 2, there was prepared (4-{[4-(3-(2-methylphenyl)ureido)-phenyl]-acetyl}-homopiperazin-1-yl)-acetic acid (Compound LV). MS: $MH^+$ 425. HPLC: $R_T$=9.92 minutes.

By proceeding in a similar manner but using α-bromophenylacetic acid in step 1 and using homopiperazine in step 2 with a reaction time of 2 days, there was prepared (3-{[4-(3-(2-methylphenyl)ureido)-phenyl]-acetyl}-homopiperazin-1-yl)-phenylacetic acid (Compound LW). MS: $MH^+$ 501. HPLC:$R_T$=11.56 minutes.

## EXAMPLE 18

Compounds LX and LY

Step 1: Wang resin was treated with 4-bromobutyric acid according to the procedure described in Example 18(a).

Step 2. The resin (0.6g) from step 1 was treated with a mixture of piperazine (0.6g) and potassium iodide (0.1g) in dimethylsulphoxide (6ml). The mixture was heated at 80°C for 3 - 4 hours in a sealed tube. After cooling to room temperature the resin was drained, then washed twice with dimethylsulphoxide, then three times with dimethylformamide, then three times with tetrahydrofuran, then three times with dichloromethane, then sucked dry, and then dried under high vacuum.

Step 3. The resin from step 2 (50mg, nominal 0.046mmol/g loading) was treated successively at room temperature with a solution of 4-[3-(2-methylphenyl)ureido]-phenylacetic acid (0.092mmol) in dimethylformamide (0.75ml), then with diisopropylethylamine (50μl) and then with a solution of O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (0.092mmol) in dimethylformamide (0.75ml). The mixture was kept at room temperature for 1-2 hours, then the resin drained, and then washed three times with dimethylformamide, three times with tetrahydrofuran, three times with dichloromethane, and dried under high vacuum.

Step 4. The resin from step 3 was treated with a mixture of trifluoroacetic acid and dichloromethane (2ml , 1:1, v/v). After 1-2 hours at room temperature the resin was drained and then washed with a mixture of trifluoroacetic acid and dichloromethane (2ml). The combined filtrate and washings were evaporated to give (4-{[4-(3-(2-methylphenyl)ureido)-phenyl]-acetyl}-piperazin-1-yl)-butyric acid (Compound LX). MS: $MH^+$ 439. HPLC retention time=11.23 minutes [HPLC column 5 micron Hypersil Elite C18 operated under gradient elution conditions

with a mixture of acetonitrile and water plus 0.1% trifluoroacetic acid as the mobile phase (0-3 minutes 20% acetonitrile; 3-14 minutes ramp up to 80% acetonitrile; 15 minutes to end of run 80% acetonitrile) and UV detection at 220nm].

(b) By proceeding in a similar manner but using homopiperazine in step 2, there was prepared (4-{[4-(3-(2-methylphenyl)ureido)-phenyl]-acetyl}-homopiperazin-1-yl)-butyric acid (Compound LY). MS: $MH^+$ 453. HPLC retention time=11.21 minutes.

## EXAMPLE 19

Compounds LZ, MA and MB

Step 1. The resin from Step 1 Example 17(a) (0.5g, 0.92mmol/g loading) was treated with a mixture of 4-[(3,4-dimethoxybenzylidenamino)methyl]piperidine (1.0g) and diisopropylethylamine (500µl) in dimethylsulphoxide (10ml). After standing at room temperature overnight the resin was drained, then washed three times with dimethylformamide, then three times with tetrahydrofuran, then three times with dichloromethane, then sucked dry, and then dried under high vacuum.

Step 2. The resin from Step 1 (50mg, 0.046 mmol/g loading) was suspended in a mixture of acetonitrile, water and trifluoroacetic acid (2.5ml, 80:20:2, v/v/v) at room temperature. The mixture was kept at room temperature until HPLC analysis of the supernatant solution showed no more 3,4-dimethoxybenzaldehyde was being produced. The resin was then drained, then washed three times with acetonitrile, then three times with dimethylformamide, then twice with 5 % DIPEA in dimethylformamide, then three times with dimethylformamide, then three times with tetrahydrofuran, then three times with dichloromethane, then sucked dry and then dried under high vacuum.

Step 3. The resin from step 2 (50mg, nominal 0.046mmol/g loading) was treated successively at room temperature with a solution of 4-[3-(2-methylphenyl)ureido]-phenylacetic acid (0.092mmol) in dimethylformamide (0.75ml), then with diisopropylethylamine (50µl) and then with a solution of O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (0.092mmol) in dimethylformamide (0.75ml). The mixture was kept at room temperature for 1-2 hours, then the resin drained, and then washed three times with dimethylformamide, three times with tetrahydrofuran, three times with dichloromethane, and dried under high vacuum.

Step 4. The resin from step 3 was treated with a mixture of trifluoroacetic acid and dichloromethane (2 ml , 1:1, v/v). After 1 -2 hours at room temperature the resin was drained and then washed with a mixture of trifluoroacetic acid and dichloromethane (2ml). The combined filtrate and washings were evaporated to give 3-(4-{[4-(3-(2-methylphenyl)ureido)-phenyl]-acetylaminomethyl}-piperidin-1-yl)-propionic acid (Compound LZ). MS: $MH^+$ 453. HPLC: $R_T$=10.06 minutes [HPLC column 5 micron Hypersil Elite C18 operated under gradient elution conditions with a mixture of acetonitrile and water plus 0.1% trifluoroacetic acid as the mobile phase (0-3 minutes 20% acetonitrile; 3-14 minutes ramp up to 80% acetonitrile; 15 minutes to end of run 80% acetonitrile) and UV detection at 220nm].

By proceeding in a similar manner but using (R,S)-3-(3,4-dimethoxybenzylidenamino)-pyrrolidine in step 1, there was prepared 3-(4-{[4-(3-(2-methylphenyl)ureido)-phenyl]-acetylamino}-pyrrolidin-1-yl)-propionic acid (Compound MA). MS: $MH^+$ 425. HPLC: $R_T$=4.51 minutes [with a 6 minute integration inhibition].

By proceeding in a similar manner but using 3-methoxy-4-[3-(2-methylphenyl)ureido]-phenylacetic acid in step 3, there was prepared 3-(4-{[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylaminomethyl}-piperidin-1-yl)-propionic acid (Compound MB). MS: $MH^+$ 497. HPLC: $R_T$=15.04 minutes [HPLC column Dynamax 60angstrom C18 column operated under gradient elution conditions with a mixture of acetonitrile and water plus 0.1% trifluoroacetic acid as the mobile phase (0-20 minutes 0% acetonitrile, ramped up to 100% acetonitrile after 20 minutes, then maintained at 100% acetonitrile) and UV detection at 220nm.]

## EXAMPLE 20

Compounds MC to MG

Step 1. The resin from step 1 Example 18(a) (0.75g, nominal 0.92mmol/g loading) was treated with 4-[(3,4-dimethoxybenzylidenamino)methyl]piperidine (1.5g, Reference Example 15) and DIPEA (750μL) in dimethylsulphoxide (15ml). After standing at room temperature overnight the resin was drained, then washed three times with dimethylformamide, then three times with tetrahydrofuran, then three times with dichloromethane, then sucked dry, and then dried under high vacuum.

Step 2. The resin from Step 1 (50mg, 0.046 mmol/g loading) was suspended in a mixture of acetonitrile, water and trifluoroacetic acid (2.5ml, 80:20:2, v/v/v) at room temperature. The mixture was kept at room temperature until HPLC analysis of the supernatant solution showed

no more 3,4-dimethoxybenzaldehyde was being produced. The resin was then drained, then washed three times with acetonitrile, then three times with dimethylformamide, then twice with 5 % diisopropylethylamine in dimethylformamide, then three times with dimethylformamide, then three times with tetrahydrofuran, then three times with dichloromethane, then sucked dry and then dried under high vacuum.

Step 3. The resin from step 2 (50mg, nominal 0.046mmol/g loading) was treated successively at room temperature with a solution of 4-[3-(2-methylphenyl)ureido]-phenylacetic acid (0.092mmol) in dimethylformamide (0.75ml), then with diisopropylethylamine (50µl) and then with a solution of O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (0.092mmol) in dimethylformamide (0.75ml). The mixture was kept at room temperature for 1-2 hours, then the resin drained, and then washed three times with dimethylformamide, three times with tetrahydrofuran, three times with dichloromethane, and dried under high vacuum.

Step 4. The resin from step 3 was treated with a mixture of trifluoroacetic acid and dichloromethane (2 ml , 1:1, v/v). After 1 -2 hours at room temperature the resin was drained and then washed with a mixture of trifluoroacetic acid and dichloromethane (2ml). The combined filtrate and washings were evaporated to give (4-{[4-(3-(2-methylphenyl)ureido)-phenyl]-acetylaminomethyl}-piperidin-1-yl)-acetic acid (Compound MC). MS: $MH^+$ 439. HPLC retention time=9.99 minutes [HPLC column 5 micron Hypersil Elite C18 operated under gradient elution conditions with a mixture of acetonitrile and water plus 0.1% trifluoroacetic acid as the mobile phase (0-3 minutes 20% acetonitrile; 3-14 minutes ramp up to 80% acetonitrile; 15 minutes to end of run 80% acetonitrile) and UV detection at 220nm].

(b) By proceeding in a similar manner but using (R,S)-3-(3,4-dimethoxybenzylidenamino)-pyrrolidine in step 1, there was prepared (3-{[4-(3-(2-methylphenyl)ureido)-phenyl]-acetylamino}-pyrrolidin-1-yl)-acetic acid (Compound MD). MS: $MH^+$ 397. HPLC: $R_T$=3.87 minutes [with a 6 minute integration inhibition].

(c) By proceeding in a similar manner but using [3-(3,4-dimethoxybenzylidenamino)propyl]-methylamine in step 1, there was prepared [3-{[4-(3-(2-methylphenyl)ureido)-phenyl]-acetylamino}-propyl]-methylamino-acetic acid (Compound ME). MS: $MH^+$ 413. HPLC: $R_T$=13.52 minutes.

(d) By proceeding in a similar manner but using 3-[3-(2-methylphenyl)-ureido]phenylacetic acid in step 3, there was prepared (4-{[3-(3-(2-methylphenyl)ureido)-phenyl]-acetylaminomethyl}-piperidin-1-yl)-acetic acid (Compound MF). MS: $MH^+$ 413. HPLC: $R_T$=13.52 minutes.

(e) By proceeding in a similar manner but using 3-[4-(3-(2-methylphenyl)-ureido)phenyl]-propionic acid in step 3, there was prepared [3-{3-[4-(3-(2-methylphenyl)ureido)-phenyl]-propionylamino}-propyl]-methylamino-acetic acid (Compound MG). MS: $MH^+$ 413. HPLC: $R_T$=13.60 minutes.

## EXAMPLE 21

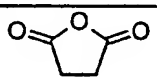
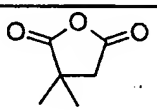
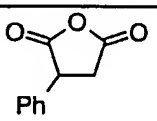
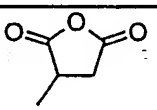
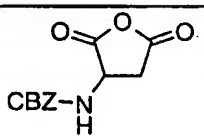
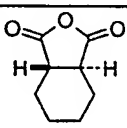
Compounds LG and MH to NJ

To a solution of 1-[4-(2-[1,4]diazepan-1-yl-2-oxo-ethyl)-2-methoxy-phenyl]-3-o-tolyl-urea [0.1mmol, Reference Example 16] and diisopropylethylamine (0.1mmol) in tetrahydrofuran (2ml) was added 3-methylglutaric anhydride (0.1mmol) in tetrahydrofuran (1ml). The mixture was left at room temperature for 48 hours then concentrated to afford 5-(4-{[3-methoxy-4-(3-o-tolyl-ureido)-phenyl]-acetyl}-[1,4]diazepan-1-yl)-3-methyl-5-oxo-pentanoic acid (Compound LG) as an oil. HPLC: $R_T$=3.1 minutes. MS: 525 ($MH^+$).

By proceeding in a manner similar but replacing 3-methylglutaric anhydride with the anhydrides shown in Table 10 there were prepared Compounds MH to MU.

By proceeding in a manner similar but replacing 1-[4-(3-[1,4]diazepan-1-yl-3-oxo-propyl)-2-methoxy-phenyl]-3-o-tolyl-urea in place of 1-[4-(2-[1,4]diazepan-1-yl-2-oxo-ethyl)-2-methoxy-phenyl]-3-o-tolyl-urea and replacing 3-methylglutaric anhydride with the anhydrides shown in Table 10 there were prepared Compounds MV to NJ.

TABLE 10

| Compound number | Product | HPLC $R_T$ (minutes) | MS $M^+$ | Anhydride used to replace 3-methylglutaric anhydride |
|---|---|---|---|---|
| Compound MH | 4-(4-{[3-methoxy-4-(3-o-tolyl-ureido)-phenyl]-acetyl}-[1,4]diazepan-1-yl)-4-oxo-butanoic acid. | 2.99 | 497 |  |
| Compound MI | 4-(4-{[3-methoxy-4-(3-o-tolyl-ureido)-phenyl]-acetyl}-[1,4]diazepan-1-yl)-4-oxo-3,3-dimethylbutanoic acid. | 3.2 | 525 |  |
| Compound MJ | 4-(4-{[3-methoxy-4-(3-o-tolyl-ureido)-phenyl]-acetyl}-[1,4]diazepan-1-yl)-4-oxo-3-phenylbutanoic acid. | 3.45 | 573 |  |
| Compound MK | 4-(4-{[3-methoxy-4-(3-o-tolyl-ureido)-phenyl]-acetyl}-[1,4]diazepan-1-yl)-4-oxo-3-methylbutanoic acid. | 3.09 | 511 |  |
| Compound ML | 4-(4-{[3-methoxy-4-(3-o-tolyl-ureido)-phenyl]-acetyl}-[1,4]diazepan-1-yl)-4-oxo-3-(carbobenzyloxy)-butanoic acid. | 3.5 | 646 |  |
| Compound MM | 2-(4-{[3-methoxy-4-(3-o-tolyl-ureido)-phenyl]-acetyl}-[1,4]diazepan-1-carbonyl)-cyclohexane-carboxylic acid. | 3.36 | 551 |  |

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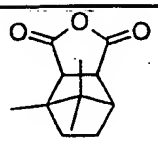
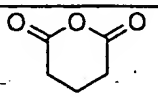
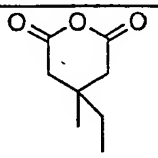
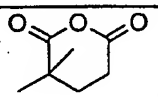
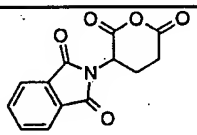
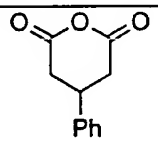
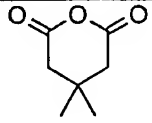
|---|---|---|---|---|
| Compound MN | 3-(4-{[3-methoxy-4-(3-o-tolyl-ureido)-phenyl]-acetyl}-[1,4]diazepan-1-carbonyl)-4,7,7-trimethylbicyclo[2.2.1]heptane-2-carboxylic acid. | 3.35 | 579 |  |
| Compound MO | 5-(4-{[3-methoxy-4-(3-o-tolyl-ureido)-phenyl]-acetyl}-[1,4]diazepan-1-yl)-5-oxo-pentanoic acid. | 3.02 | 511 |  |
| Compound MP | 5-(4-{[3-methoxy-4-(3-o-tolyl-ureido)-phenyl]-acetyl}-[1,4]diazepan-1-yl)-3-ethyl-3-methyl-5-oxo-pentanoic acid. | 3.45 | 553 |  |
| Compound MQ | 5-(4-{[3-methoxy-4-(3-o-tolyl-ureido)-phenyl]-acetyl}-[1,4]diazepan-1-yl)-5-oxo-2,2-dimethylpentanoic acid | 3.2 | 539 |  |
| Compound MR | 5-(4-{[3-methoxy-4-(3-o-tolyl-ureido)-phenyl]-acetyl}-[1,4]diazepan-1-yl)-2-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-5-oxo-pentanoic acid | 3.32 | 656 |  |
| Compound MS | 5-(4-{[3-methoxy-4-(3-o-tolyl-ureido)-phenyl]-acetyl}-[1,4]diazepan-1-yl)-5-oxo-3-phenylpentanoic acid | 3.38 | 587 |  |
| Compound MT | 5-(4-{[3-methoxy-4-(3-o-tolyl-ureido)-phenyl]-acetyl}-[1,4]diazepan-1-yl)-3-ethyl-3,3-dimethyl-5-oxo-pentanoic acid | 3.32 | 539 |  |

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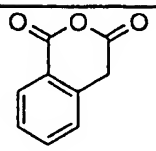
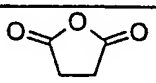
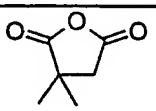
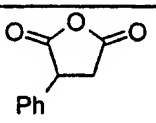
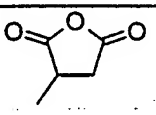
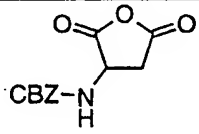
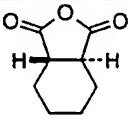
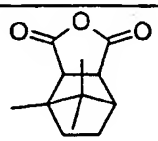
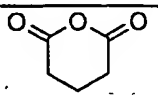
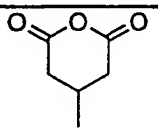
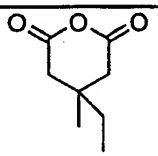
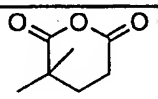
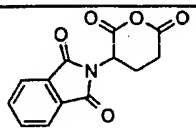
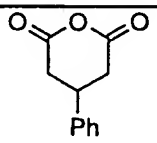
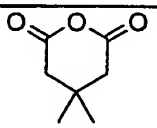
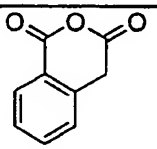
| Compound MU | 2-[5-(4-{[3-methoxy-4-(3-o-tolyl-ureido)-phenyl]-acetyl}-[1,4]diazepan-1-yl)-2-oxo-ethyl]-benzoic acid | 3.37 | 559 |  |
| Compound MV | 4-(4-{3-[3-methoxy-4-(3-o-tolyl-ureido)-phenyl]-propionyl}-[1,4]diazepan-1-yl)-4-oxo-butanoic acid. | 3.09 | 511 |  |
| Compound MW | 4-(4-{3-[3-methoxy-4-(3-o-tolyl-ureido)-phenyl]-propionyl}-[1,4]diazepan-1-yl)-4-oxo-3,3-dimethylbutanoic acid. | 3.29 | 539 |  |
| Compound MX | 4-(4-{3-[3-methoxy-4-(3-o-tolyl-ureido)-phenyl]-propionyl}-[1,4]diazepan-1-yl)-4-oxo-3-phenylbutanoic acid. | 3.53 | 587 |  |
| Compound MY | 4-(4-{3-[3-methoxy-4-(3-o-tolyl-ureido)-phenyl]-propionyl}-[1,4]diazepan-1-yl)-4-oxo-3-methylbutanoic acid. | 3.18 | 525 |  |
| Compound MZ | 4-(4-{3-[3-methoxy-4-(3-o-tolyl-ureido)-phenyl]-propionyl}-[1,4]diazepan-1-yl)-4-oxo-3-(carbobenzyloxy)-butanoic acid. | 3.57 | 660 |  |
| Compound NA | 2-(4-{3-[3-methoxy-4-(3-o-tolyl-ureido)-phenyl]-propionyl}-[1,4]diazepan-1-carbonyl)-cyclohexane-carboxylic acid. | 3.44 | 565 |  |

| | | | | |
|---|---|---|---|---|
| Compound NB | 3-(4-{3-[3-methoxy-4-(3-o-tolyl-ureido)-phenyl]-propionyl}-[1,4]diazepan-1-carbonyl)-4,7,7-trimethylbicyclo[2.2.1]heptane-2-carboxylic acid. | 3.42 | 593 |  |
| Compound NC | 5-(4-{3-[3-methoxy-4-(3-o-tolyl-ureido)-phenyl]-propionyl}-[1,4]diazepan-1-yl)-5-oxo-pentanoic acid. | 3.14 | 525 |  |
| Compound ND | 5-(4-{3-[3-methoxy-4-(3-o-tolyl-ureido)-phenyl]-propionyl}-[1,4]diazepan-1-yl)-3-methyl-5-oxo-pentanoic acid. | 3.2 | 539 |  |
| Compound NE | 5-(4-{3-[3-methoxy-4-(3-o-tolyl-ureido)-phenyl]-propionyl}-[1,4]diazepan-1-yl)-3-ethyl-3-methyl-5-oxo-pentanoic acid | 3.54 | 567 |  |
| Compound NF | 5-(4-{3-[3-methoxy-4-(3-o-tolyl-ureido)-phenyl]-propionyl}-[1,4]diazepan-1-yl)-2,2-dimethyl-5-oxo-pentanoic acid | 3.31 | 553 |  |
| Compound NG | 5-(4-{3-[3-methoxy-4-(3-o-tolyl-ureido)-phenyl]-propionyl}-[1,4]diazepan-1-yl)-2-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-5-oxo-pentanoic acid | 3.41 | 670 |  |

| | | | | |
|---|---|---|---|---|
| Compound NH | 5-(4-{3-[3-methoxy-4-(3-o-tolyl-ureido)-phenyl]-propionyl}-[1,4]diazepan-1-yl)-5-oxo-3-phenylpentanoic acid | 3.44 | 601 |  |
| Compound NI | 5-(4-{3-[3-methoxy-4-(3-o-tolyl-ureido)-phenyl]-propionyl}-[1,4]diazepan-1-yl)-3,3-dimethyl-5-oxo-pentanoic acid | 3.39 | 553 |  |
| Compound NJ | 2-[5-(4-{3-[3-methoxy-4-(3-o-tolyl-ureido)-phenyl]-propionyl}-[1,4]diazepan-1-yl)-2-oxo-ethyl]-benzoic acid | 3.44 | 573 |  |

## EXAMPLE 22

Compound NK

A solution of 2-benzyloxycarbonylamino-3-[4-({2-[3-methoxy-4-(3-o-tolyl-ureido)-phenyl]-acetylamino}-methyl)-piperidin-1-yl]-propionic acid ethyl ester [Reference Example18, 0.17g] in 1M sodium hydroxide (0.78ml) and methanol (2ml) was heated at 40 $^{0}$C for 10h. The mixture was neutralised to pH 6 with 1M hydrochloric acid and extracted with ethyl acetate (3x 20ml). The solution was concentrated to low volume and subjected to flash chromatography eluting with a 1:1 mixture of methanol and ethyl acetate to afford 2-benzyloxycarbonylamino-3-[4-({2-[3-methoxy-4-(3-o-tolyl-ureido)-phenyl]-acetylamino}-methyl)-piperidin-1-yl]-propionic acid (50mg, Compound NK) as a pale yellow solid. HPLC: $R_T$=14.02 minutes. HPLC conditions: Dynamax 60 angstrom C18 column; acetonitrile/water mix (both buffered with 0.1%TFA) - 0% acetonitrile for 5mins ramp up to 100% acetonitrile at 15 minutes, maintain at 100%; UV detection @ 220 nM. MS 654 ($MNa^+$,100%), 632 ($MH^+$,50%).

## EXAMPLE 23

Compound NL

A mixture of 4-({2-[3-methoxy-4-(3-o-tolyl-ureido)-phenyl]-acetylamino}-methyl)-piperidine (Reference Example 4, 200mg), glutaric anhydride (100mg), tetrahydrofuran (20ml) and dimethylformamide (5ml) was stirred at ambient temperature for 48 hours. After this time, the reaction mixture was concentrated to low volume and poured into 1.0M hydrochloric acid

(50ml). The resultant solid was collected and washed with 1.0M hydrochloric acid (10ml) and water (2x10ml). The solid was recrystallised from ethanol to leave 5-[4-({2-[3-methoxy-4-(3-o-tolyl-ureido)-phenyl]-acetylamino}-methyl)-piperidin-1-yl]-5-oxo-pentanoic acid (80mg, Compound NL) as a white solid, m.p. 177-180 °C. [Elemental analysis:- C,63.7; H,7.0; N,10.6% Calculated for $C_{28}H_{36}N_4O_6$:- C,64.1; H,6.9; N,10.7%]. MS: 525 $[MH]^+$.

## EXAMPLE 24

Compounds NM and NN

A mixture of 4-({2-[3-methoxy-4-(3-o-tolyl-ureido)-phenyl]-acetylamino}-methyl)-piperidine (Reference Example 19, 150 mg), N-(*tert*-butoxycarbonyl)-L-glutamic acid-α-benzyl ester (120mg), [O-(7-azabenzotriazol-1-yl)-1,1,3,3,-tetramethyluronium hexafluorophosphate] (120mg) and diisopropylethylamine (0.1ml) in dimethylformamide (5ml) was stirred at ambient temperature for 18 hours. After this time, the reaction mixture was poured into 1.0M hydrochloric acid (20ml) and the resultant white solid collected and washed sequentially with 10ml portions of water, saturated sodium bicarbonate and water. The resultant white solid was dissolved in ethanol (10ml) and treated with 10% palladium on charcoal (20mg). This reaction mixture was stirred at ambient temperature under an atmosphere of hydrogen for 18 hours before being filtered through a short pad of diatomaceous earth. The filtrate was concentrated to leave (*S*)-2-tert-Butoxycarbonylamino-5-[4-({2-[3-methoxy-4-(3-o-tolyl-ureido)-phenyl]-acetylamino}-methyl)-piperidin-1-yl]-5-oxo-pentanoic acid (50mg, Compound NM) as a white solid , m.p. >135 °C (with decomposition). MS: 640 $[MH]^+$.

(b) By proceeding in a similar manner to Example 4(a) but replacing N-(*tert*-butoxycarbonyl)-L-glutamic acid-α-benzyl ester with N-(*tert*-butoxycarbonyl)-D-glutamic acid-α-benzyl ester there was prepared (*R*)-2-tert-butoxycarbonylamino-5-[4-({2-[3-methoxy-4-(3-o-tolyl-ureido)-phenyl]-acetylamino}-methyl)-piperidin-1-yl]-5-oxo-pentanoic acid (Compound NN) as a white solid, m.p. >135 °C (with decomposition). MS: 640 $[MH]^+$.

## REFERENCE EXAMPLE 1

3,4-Dimethoxy-3-(N-methyl-3-aminopropylimino) benzene

A mixture of 3,4-dimethoxy- benzaldehyde (38.2g) in toluene (450ml) was treated with N-methyl-1,3-propanediamine (23.7ml), then heated at reflux temperature under Dean and Stark conditions for one hour and then allowed to stand overnight. The reaction mixture was evaporated to give the title compound (61g) which was used without further purification.

## REFERENCE EXAMPLE 2

Prep of 2-methoxy-phenoxypropylamine

Sodium hydride (1.6g) was added to 2-methoxyphenol (5g) in tetrahydrofuran under nitrogen and stirred for 15 minutes. N-(3-bromopropyl)phthalimide (11.26g) was added in tetrahydrofuran (40ml) and the reaction heated at reflux for 6 hours. The solvent was removed under reduced pressure, the residue dissolved in dichloromethane and the organic layer separated, washed with 1M NaOH and saline then dried with magnesium sulphate, filtered and the filtrate concentrated under reduced pressure to give N-[3-(2-methoxyphenoxy)propyl]-phthalimide as a pale yellow solid. N-[3-(2-methoxyphenoxy)propyl]phthalimide (8g) was suspended in ethanol (40ml) and hydrazine hydrate (1.28g) added and the mixture refluxed for 1 hour to give a thick white paste. HCl was then added (7.2ml of 18% HCl(aq)) ands the mixture refluxed for a further hour. After cooling the resulting solid was filtered and washed with ethanol. The filtrate was concentrated under reduced pressure and basified with 1M sodium hydroxide and then extracted with dichloromethane and then dried with magnesium sulphate, filtered and the filtrate concentrated under reduced pressure to give 2-methoxyphenoxy)-propylamine as a pale brown oil.

## REFERENCE EXAMPLE 3

Prep of Fmoc-3-oxopiperazin-2-yl-acetic acid

Dimethyl malonate (66.96g) and ethylenediamine (23.5g) were dissolved in 2-propanoland heated to 55°C for 16hours. The solvent was removed under reduced pressure and the resulting white solid was recrystallised from acetone to give methyl-3-oxopiperazin-2-yl-acetate as white crystals (60.5g).

To sodium hydroxide (20.9g) in water (80ml) was added methyl-3-oxopiperazin-2-yl-acetate (30g). The mixture was stirred overnight and the methanol then removed under reduced pressure. Water (100ml) was added and the pH was adjusted to pH1 with 1N HCl and the resulting oil extracted into ethyl acetate. The organics were separated, dried with anhydrous magnesium sulphate, filtered and the filtrate reduced under vacuum to give 3-oxopiperazin-2-yl-acetic acid.

3-Oxopiperazin-2-yl-acetic acid (20g) was added to sodium hydrogen carbonate (17.5g), N-(9-fluorenylmethoxycarbonyloxy)succinimide (35g), acetone (300ml) and water (80ml). The mixture was stirred for 16 hours and the resulting solid filtered, washed with water and dried under vacuum to give fmoc-3-oxopiperazin-2-yl-acetic acid.

## REFERENCE EXAMPLE 4

Preparation of Fmoc-4-phenyl-piperazin-2-yl-acetic acid

N-Phenyl-N'-(triphenylmethyl)ehane-1,2-diamine (5g) (J. Chem. Soc. Perkin I., 1035 (1992)) was added to methyl-4-bromocrotonate (2.78g) in acetone (120ml) and anhydrous potassium carbonate (3.6g). After stirring for 18hours the mixture was filtered and the filtrate concentrated under reduced pressure to give methyl-4-{N-phenyl-N-[2-(triphenylmethylamino)ethyl]amino}but-2-oate as a yellow oil.

Methyl-4-{N-phenyl-N-[2-(triphenylmethylamino)ethyl]amino}but-2-oate (1.97g) was dissolved in methanol (18ml) and HCl added (4M in dioxan, 18ml). After refluxing for 20 minutes the mixture was neutralised with potassium carbonate and extracted with dichloromethane. The combined extract was dried with anhydrous magnesium sulphate, filtered and the filtrate reduced under vacuum to give methyl-4-phenylpiperazine-2-yl-acetate (860mg) as a pale yellow oil after chromatography.

To potassium hydroxide (1.44g) in water (30ml) and methanol (50ml) was added methyl-4-phenylpiperazine-2-yl-acetate (2g). The mixture was stirred for 45 minutes and the methanol then removed under reduced pressure and the pH was adjusted to pH3 by addition of concentrated hydrochloric acid and the solution concentrated under vacuum to give 4-phenylpiperazine-2-yl-acetic acid.

4-Phenylpiperazine-2-yl-acetic acid (2.19g) was added to sodium hydrogen carbonate (2.16g), N-(9-fluorenylmethoxycarbonyloxy)succinimide (2.88g), acetone (25ml) and water (30ml). The mixture was stirred for 19 hours the acetone was removed under reduced pressure. The mixture was acidified to pH3 with citric acid (10% in water). and the resulting solid extracted into dichloromethane, dried with anhydrous magnesium sulphate, filtered and the filtrate reduced under vacuum to give Fmoc-4-phenyl-piperazin-2-yl-acetic acid as a white foam (3.4g).

## REFERENCE EXAMPLE 5

Prep of [1,4]diazepane-1-carbonyl)-amino]-pentanedioic acid

Dimethyl-3-oxoglutonate (26.1g) and ammonium acetate (120g) in methanol (400ml) was stirred over 3A molecular sieves for 2 days. The solution was filtered and the pH adjusted to 3.0 using HCl (4M in dioxan). Sodium cyanoborohydride (11.8g) was added and the mixture stirred for 1 hour. The solvent was removed under reduced pressure and the pH adjusted to pH9. Water (200ml) was added an the organics extracted into dichloromethane. The organics were dried with anhydrous magnesium sulphate, filtered and the filtrate reduced under vacuum to give a clear oil that was distilled (0.4mmHg, 87oC) to give dimethyl-3-aminopentanedioate.

Homopiperazine was loaded onto a nitrophenylcarbonate activated Wang resin (Dixit D M, Leznoff C C, Isr J Chem, 17() p. 248, 1978). The resin(1g) was treated with dichloromethane

(15ml), diisopropylethylamine (1.75ml) and phosgene (1.93M solution in toluene, 5mls) and the resin shaken for 1.5 hours. The resin was washed six times with dichloromethane, and then twice with dimethylformamide. Then dimethylformamide (10ml) was added and triethylamine (0.75ml) and dimethyl-3-aminopentanedioate and the mixture shaken for 1 hour and allowed to stand for 3 days. The resin was drained and washed six times with dimethylformamide, and then three times with methanol , dichloromethane and finally with diethyl ether before drying under vacuum. The resin was then treated with a mixture of trifluoroacetic acid, dichloromethane, water (35:15:5, 20ml) for one hour. The resin was then filtered and the filtrate reduced under nitrogen to give [1,4]diazepane-1-carbonyl)-amino]-pentanedioic acid as a brown oil.

## REFERENCE EXAMPLE 6

Ethyl-3-(2,4-dioxo-3,4-dihydro-2H-pyrimidin-1yl)-propionate

Uracil (5g) was refluxed for 16 hours with ethyl acrylate (4.5g) and sodium ethoxide (300mg) in ethanol (100ml). The remaining solid was filtered off and Dowex-50 resin (10g) was added. The resin was removed by filtration and the remaining liquor reduced under vacuum to give solid ethyl-3-(2,4-dioxo-3,4-dihydro-2H-pyrimidin-1yl)-propionate (9g).

## REFERENCE EXAMPLE 7

Ethyl-3-(Chloro-2-oxo-2Hpyrimidin-1-yl)-propionate

Ethyl-3-(2,4-dioxo-3,4-dihydro-2H-pyrimidin-1yl)-propionate (5g) and phosphorous oxychloride (11.6ml) were stirred at 70°C for 4 hours. Excess phosphorous oxychloride was removed under vacuum and the remaining oil cooled to 0°C and neutralised with 5% aqueous sodium hydrogen carbonate. The resulting solid was filtered off , dissolved in acetonitrile, dried with anhydrous magnesium sulphate, filtered and the filtrate reduced under vacuum to give ethyl-3-(chloro-2-oxo-2Hpyrimidin-1-yl)-propanoate (3g).

## REFERENCE EXAMPLE 8

1-(4-{[3-methoxy-4-(3-o-tolylureido)phenyl]acetyl}-[1,4]-diazepane-1-carbonyl)piperidine-4-carboxylic acid ethyl ester

Diisopropylethylamine (8.06mL) was added to a stirred solution of ethyl 1-([1,4]-diazepane-1-carbonyl)piperidine-4-carboxylate hydrochloride (1.23g, Reference Example 9) in dimethylformamide (95mL). After 10min of 3-methoxy-4-[3-(2-methylphenyl)ureido]-phenylacetic acid (1.22g) and O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (1.47g) were added sequentially. The mixture was stirred for 5h, then allowed to stand overnight at room temperature. After evaporation of the solvents the residue was dissolved in ethyl acetate and washed with5% aqueous sodium carbonate, then water and

dried over magnesium sulphate. Removal of the solvent afforded a yellow gum which was subjected to flash chromatography (silica, ethyl acetate then 5% methanol in ethyl acetate as eluents) to give the title compound (231mg).

## REFERENCE EXAMPLE 9

Ethyl 1-([1,4]-diazepane-1-carbonyl)piperidine-4-carboxylate hydrochloride

4M hydrogen chloride in 1,4-dioxan (10mL) was added to a solution of 4-[4-ethoxy carbonylpiperidine-1-carbonyl]-[1,4]-diazepane-1-carboxylic acid tert butyl ester (1.48g, Reference Example 10) in ethanol (50mL) and the mixture stirred for 2 hours. Another aliquot of 4M hydrogen chloride in 1,4-dioxan (10mL) was added and stirring continued for 5 hours. The mixture was evaporated to give the title compound.

## REFERENCE EXAMPLE 10

4-[4-Ethoxy carbonylpiperidine-1-carbonyl]-[1,4]-diazepane-1-carboxylic acid tert butyl ester

A solution of ethyl 1-(4-nitrophenyloxycarbonyl)piperidine-4-carboxylate as a pale yellow solid (1.61g, Reference Example 11) in dimethylformamide (10mL) was treated with triethylamine (4.86mL) then with a solution of N-(t-butoxycarbonyl)-homopiperazine (1g) in dimethylformamide (10mL). The mixture was stirred at room temperature for 5hours, then at 60°C for 5 hours, then at 100°C for 2hours and then at reflux for 9 hours. The reaction mixture was evaporated and the residue was dissolved in ethyl acetate. The solution was washed with aqueous sodium bicarbonate (10% ) then with and brine and dried ($MgSO_4$). Evaporation of the solvent gave the title compound (1.48g) as an oil.

## REFERENCE EXAMPLE 11

Ethyl 1-(4-nitrophenyloxycarbonyl)piperidine-4-carboxylate

A solution of 4-nitrophenyl chloroformate (19.63g) in dichloromethane (150mL), under a nitrogen atmosphere, was treated dropwise with ethyl isonipecotate (15g) in a mixture of dichloromethane (150mL) and diisopropylethylamine (33.93mL), whilst keeping the reaction mixture at -15°C. After stirring at room temperature for 4 hours and then standing for at room temperature 16 hours the reaction mixture was washed with aqueous sodium bicarbonate solution (10%), then with brine, then dried over magnesium sulphate and then evaporated. The residue was subjected to flash chromatography on silica using gradient elution with a mixture of ethyl acetate and pentane (1:5 to 3:10, v/v) to give the title compound (24.1g) as a pale yellow solid.

## REFERENCE EXAMPLE 12

Ethyl-(4-{2-[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylamino}-piperidin-1-yl)-acetate

A solution of 4-{2-[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylamino}-piperidine (0.67g, Reference Example 13) and diisopropylamine (2.96g) in dry dimethylformamide (75ml) was treated with ethyl bromoacetate (0.28g). After stirring at room temperature for 18 hours an additional quantity of ethyl bromoacetate (80mg) was added and stirring was continued for an additional 4 hours. The reaction mixture was diluted with ethyl acetate (300ml) and then the solution was washed twice with 0.4% sodium hydrogen carbonate (100ml), then dried over magnesium sulphate and then evaporated. The residue was subjected to flash chromatography on silica, using a gradient elution using ethyl acetate to 10% methanol in ethyl acetate, to give the title compound (0.23g) as a foam.

## REFERENCE EXAMPLE 13

4-{2-[3-Methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylamino}-piperidine

A solution of 1-benzyl-4-{2-[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylamino}-piperidine [4g, Reference Example 14] in a mixture of ethanol and acetic acid (300ml , 5:1, v/v) was hydrogenated at 2 bar hydrogen pressure in the presence of 5% palladium on carbon for 18 hours. The reaction mixture was filtered through Hyflo Super Cel ® and the filter pad was washed with ethanol (250ml). The combined filtrate and washings were evaporated to afford the title compound (2.5g) as an off-white foam. MS: $M^+$ 397 (100%).

## REFERENCE EXAMPLE 14

1-Benzyl-4-{2-[3-methoxy-4-(3-(2-methylphenyl)ureido)-phenyl]-acetylamino}-piperidine

A solution of 3-methoxy-4-[3-(2-methylphenyl)ureido]phenylacetic acid (2g, prepared as described in Example 52B of International Patent Application Publication No. WO 96/22966), diisopropylethylamine (2.44ml) in dry dimethylformamide was treated with [O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (2.54g) followed by 4-amino-1-benzylpiperidine (1.3ml). After stirring at room temperature for 30 minutes the reaction mixture was evaporated and then treated with ethyl acetate (300ml). The solution was washed with saturated sodium hydrogen carbonate (200ml), then with water (100ml), then dried over magnesium sulphate and then evaporated to give the title compound (3g) as an orange foam which was used without further purification. MS: $M^+$ 487 (100%).

## REFERENCE EXAMPLE 15

(a) 4-[(3,4-dimethoxybenzylideneamino)methyl]piperidine

A solution of 4-aminomethylpiperidine (14.4g) in toluene (150ml) was treated with 3,4-dimethoxybenzaldehyde (20.9g) at room temperature and the resulting mixture was heated at reflux for 3 hours with the aid of a Dean-Stark trap for water removal. The reaction mixture was evaporated to give the title compound (33g) as an off white solid which was used without further purification.

(b) By proceeding in a similar manner to Reference Example 15(a), but using (R,S)-3-aminopyrrolidine, there was prepared (R,S)-3-(3,4-dimethoxybenzylidene-amino)pyrrolidine.

(c) By proceeding in a similar manner to Reference Example 15(a), but using 3-aminopropylmethylamine, there was prepared [3-(3,4-dimethoxybenzylidene-amino)propyl]methylamine.

## REFERENCE EXAMPLE 16

(a) 4-{[3-Methoxy-4-(3-o-tolyl-ureido)-phenyl]-acetyl}-[1,4]diazepane

To an ice cooled solution of 4-{[3-methoxy-4-(3-o-tolyl-ureido)-phenyl]-acetyl}-[1,4]diazepane-1-carboxylic acid tert-butyl ester [Reference Example 17(a)] (2.5g) in dry dichloromethane (120ml) was added trifluoroacetic acid (40ml). The solution was stirred at 0°C for 2 hours and the solvent removed under vacuum. The residue was taken up in dichloromethane (200ml) and washed with 1M sodium hydroxide (50ml). The aqueous layer was washed with tetrahydrofuran (200ml) which was then washed with saturated brine. The combined organic layers were dried with magnesium sulphate, filtered and evaporated to afford the title compound (1.8g) as a light brown oil. MS: 519 ($MNa^+$,24%), 497 ($MH^+$,30%), 441 ($M-C4H9^+$,50%).

(b) By proceeding in a manner similar to Reference Example 16(a) but replacing 4-{[3-methoxy-4-(3-o-tolyl-ureido)-phenyl]-acetyl}-[1,4]diazepane-1-carboxylic acid tert-butyl ester with 4-{[3-methoxy-4-(3-o-tolyl-ureido)-phenyl]-propionyl}-[1,4]diazepane-1-carboxylic acid tert-butyl ester [Reference Example 17(b)], there was prepared 4-{[3-Methoxy-4-(3-o-tolyl-ureido)-phenyl]-propionyl}-[1,4]diazepane in 62% yield. MS: 533 ($MNa^+$ ,28%), 511 ($MH^+$ ,21%), 455 ($M-C4H9^+$,47%), 411 ($M-C5H9O2^+$, 65%).

## REFERENCE EXAMPLE 17

(a) 4-{[3-Methoxy-4-(3-o-tolyl-ureido)-phenyl]-acetyl}-[1,4]diazepane-1-carboxylic acid tert-butyl ester

To a solution of [3-methoxy-4-(3-o-tolyl-ureido)-phenyl]-acetic acid (2g) in dry dimethylformamide (50ml) was added o-(7-azabenzotriazol-1-yl)1,1,3,3-tetramethyluronium hexafluorophosphate (2.54g) and the mixture stirred for 10 minutes. Diisopropylethylamine (3.3ml) followed by tert-butyl-1-homopiperazine (1.27g) were added and the reaction stirred at room temperature for 3 hours. The reaction was concentrated *in vacuo* and treated with 10% sodium carbonate solution. The aqueous layer was decanted. The residue was taken up in tetrahydrofuran (50ml) and dried over magnesium sulphate. Filtration and evaporation afforded the title compound (3g) as an orange oil. MS: 397 ($MH^+$ ,100%).

(b) By proceeding in a manner similar to Reference Example 17(a) but replacing [3-methoxy-4-(3-o-tolyl-ureido)-phenyl]-acetic acid with [3-methoxy-4-(3-o-tolyl-ureido)-phenyl]-propionic acid there was prepared 4-{[3-Methoxy-4-(3-o-tolyl-ureido)-phenyl]-propionyl}-[1,4]diazepane-1-carboxylic acid tert-butyl ester (2.9g) as an orange oil. MS: 411($MH^+$, 100%).

## REFERENCE EXAMPLE 18

2-Benzyloxycarbonylamino-3-[4-({2-[3-methoxy-4-(3-o-tolyl-ureido)-phenyl]-acetylamino}-methyl)-piperidin-1-yl]-propionic acid ethyl ester

A mixture of 4-({2-[3-methoxy-4-(3-o-tolyl-ureido)-phenyl]-acetylamino}-methyl)-piperidine [Reference Example 19, 0.542g] and aziridine-1,2-dicarboxylic acid 1-benzyl ester 2-ethyl ester [Reference Example 21, 1.03g] in dry tetrahydrofuran (20ml) and dimethylformamide (30ml) was refluxed for 72 hours. The mixture was concentrated to low volume and subjected to flash chromatography on silica eluting with ethyl acetate then with a mixture of 10:1 ethyl acetate and methanol to afford the title compound (0.15g) as a pale orange solid. MS: 660 ($MH^+$ ,100%).

## REFERENCE EXAMPLE 19

4-({2-[3-methoxy-4-(3-o-tolyl-ureido)-phenyl]-acetylamino}-methyl)-piperidine

To an ice cooled solution of 4-({2-[3-methoxy-4-(3-o-tolyl-ureido)-phenyl]-acetylamino}-methyl)-piperidine-1-carboxylic acid tert-butyl ester [Reference Example 20, 8g] in dichloromethane (120ml) was added trifluoroacetic acid (30ml). The reaction mixture was stirred at room temperature for 1.5h. The mixture was concentrated to dryness. The residue was treated with 1M sodium hydroxide (10ml) and extracted with tetrahydrofuran (5x 30ml). The organics were

washed with saturated brine and dried with magnesium sulphate. Filtration and concentration *in vacuo* afforded the title compound (6g) as a white solid, m.p. 154-160°C. MS: 411 ($MH^+$,100%).

## REFERENCE EXAMPLE 20

4-({2-[3-Methoxy-4-(3-o-tolyl-ureido)-phenyl]-acetylamino}-methyl)-piperidine-1-carboxylic acid tert-butyl ester

To a mixture of [3-methoxy-4-(3-o-tolyl-ureido)-phenyl]-acetic acid (5g), 4-aminomethyl-piperidine-1-carboxylic acid tert-butyl ester [ prepared according to the procedure described in WO9412181, 3.5g] and diisopropylethylamine (6.45g) in anhydrous dimethylformamide (150ml) was added o-(7-azabenzotriazol-1-yl)1,1,3,3-tetramethyluronium hexafluorophosphate (6.06g). The reaction mixture was stirred at room temperature for 4h and poured into 1M hydrochloric acid (700ml). The resulting solid was filtered, washed with water (5x 50ml) and dried on high vacuum to afford the title compound as a white solid which was used without further purification. MS: 511 ($MH^+$,100%) .

## REFERENCE EXAMPLE 21

Aziridine-1,2-dicarboxylic acid 1-benzyl ester 2-ethyl ester

To a solution of aziridine-2-carboxylic acid ethyl ester (prepared according to the method of Can. J. Chem. (1982), 60, 2830) in a 1:1 mixture of acetonitrile/tetrahydrofuran under a nitrogen atmosphere was added diisopropylethylamine (3.85ml) and CBZ-succinimide (5.0g). The mixture was stirred at room temperature for 24h. The reaction mixture was concentrated to low volume and diluted with ethyl acetate (150ml). The organics were washed with water (3x 100ml) and saturated brine (100ml). The solution was dried over magnesium sulphate, filtered and concentrated *in vacuo*. Purification by Mplc, eluting with 6:1 cyclohexane/ethyl acetate to afford the title compound (3g) as a yellow oil. MS: 272 ($MNa^+$,100%).

## IN VITRO AND IN VIVO TEST PROCEDURES

### 1. Inhibitory effects of compounds on VLA4 dependent cell adhesion to Fibronectin and VCAM.

#### 1.1 Metabolic labelling of RAMOS cells.

RAMOS cells (a pre-B cell line from ECACC, Porton Down, UK) are cultured in RPMI culture medium (Gibco, UK) supplemented with 5% foetal calf serum (FCS, Gibco, UK). Prior to assay

the cells are suspended at a concentration of 0.5 X $10^6$ cells/ml RPMI and labelled with 400μCi/100mls of [$^3$H]-methionine (Amersham, UK) for 18 hours at 37°C.

1.2 96 well plate preparation for adhesion assay.

Cytostar plates (Amersham, UK) were coated with 50μl/well of either 3μg/ml human soluble VCAM-1 (R&D Systems Ltd, UK) or 28.8μg/ml human tissue Fibronectin (Sigma, UK). In control non-specific binding wells 50μl phosphate buffered saline was added. The plates were then left to dry in an incubator at 25°C, overnight. The next day the plates were blocked with 200μl/well of Pucks buffer (Gibco, UK) supplemented with 1% BSA (Sigma, UK). The plates were left at room temperature in the dark for 2 hours. The blocking buffer was then disposed of and the plates dried by inverting the plate and gently tapping it on a paper tissue. 50μl/well of 3.6% dimethyl sulphoxide in Pucks buffer supplemented with 5mM manganese chloride (to activate the integrin receptor Sigma, UK) and 0.2% BSA (Sigma, UK), was added to the appropriate control test binding and non-specific binding assay wells in the plate. 50μl/well of the test compounds at the appropriate concentrations diluted in 3.6% dimethyl sulphoxide in Pucks buffer supplemented with 5mM manganese chloride and 0.2% BSA, was added to the test wells.

Metabolically labelled cells were suspended at 4 x $10^6$ cells/ml in Pucks buffer that was supplemented with manganese chloride and BSA as above. 50μl/well of cells in 3.6% dimethyl sulphoxide in Pucks buffer and supplements was added to all plate wells.

The same procedure exists for plates coated with either VCAM-1 or fibronectin and data is determined for compound inhibition of cell binding to both substrates.

1.3 Performance of assay and data analysis.

The plates containing cells in control or compound test wells are incubated in the dark at room temperature for 1 hour.

The plates are then counted on a Wallac Microbeta scintillation counter (Wallac, UK) and the captured data processed in Microsoft Excel (Microsoft, US). The data was expressed as an IC50, namely the concentration of inhibitor at which 50% of control binding occurs. The percentage binding is determined from the equation:

$$\{[(C_{TB} - C_{NS})-(C_I - C_{NS})] / (C_{TB} - C_{NS})\} X\ 100 = \%\ \text{binding}$$

where $C_{TB}$ are the counts bound to fibronectin (or VCAM-1) coated wells without inhibitor present, $C_{NS}$ are the counts present in wells without substrate, and $C_I$ are the counts present in wells containing a cell adhesion inhibitor.

Compound data of this invention is expressed for $IC_{50}$s for inhibition of cell adhesion to both fibronectin and VCAM-1. Particular compounds of the invention inhibit cell adhesion to fibronectin and VCAM-1 with IC50s in the range 100 micromolar to 1 nanomolar. Preferred compounds of the invention inhibit cell adhesion to fibronectin and VCAM-1 with IC50s in the range 30 micromolar to 0.1 nanomolar. Especially preferred compounds of the invention inhibit cell adhesion to fibronectin and VCAM-1 with IC50s in the range 100 nanomolar to 0.1 nanomolar.

2. Inhibition of antigen-induced airway inflammation in the mouse and rat.

2.1 Sensitization of the animals.

Rats (Brown Norway, Harland Olac, UK) are sensitized on days 0, 12 and 21 with ovalbumin (100 µg, intraperitoneally [i.p], Sigma, UK) administered with aluminium hydroxide adjuvant (100mg, i.p., Sigma, UK) in saline (1ml, i.p.).

In addition mice (C57) are sensitized on days 0 and 12 with ovalbumin (10µg, i.p.) administered with aluminium hydroxide adjuvant (20mg, i.p.) in saline (0.2ml, i.p.).

2.2 Antigen challenge.

Rats are challenged on any one day between days 28-38, while mice are challenged on any one day between days 20-30.

The animals are challenged by exposure for 30 minutes (rats) or 1 hour (mice) to an aerosol of ovalbumin (10g / l) generated by an ultrasonic nebulizer (deVilbiss Ultraneb, US) and passed into an exposure chamber.

2.3 Treatment protocols.

Animals are treated as required before or after antigen challenge. The aqueous-soluble compounds of this invention can be prepared in water (for oral, p.o. dosing) or saline (for intratracheal, i.t. dosing). Non-soluble compounds are prepared as suspensions by grinding and sonicating the solid in 0.5 % methyl cellulose / 0.2 % polysorbate 80 in water (for p.o. dosing, both Merck UK Ltd., UK) or saline (for i.t. dosing). Dose volumes are: for rats 1ml / kg, p.o. or 0.5mg / kg, i.t.; for mice 10ml / kg, p.o. or 1ml / kg, i.t.

2.4 Assessment of airway inflammation.

The cell accumulation in the lung is assessed 24 hours after challenge (rats) or 48-72 hours after challenge (mice). The animals are euthanized with sodium pentobarbitone (200mg/kg, i.p., Pasteur Merieux, France) and the trachea is immediately cannulated. Cells are recovered from the airway lumen by bronchoalveolar lavage (BAL) and from the lung tissue by enzymatic (collagenase, Sigma, UK) disaggregation as follows.

BAL is performed by flushing the airways with 2 aliquots (each 10 ml/kg) RPMI 1640 medium (Gibco, UK) containing 10 % fetal calf serum (FCS, Serotec Ltd., UK). The recovered BAL aliquots are pooled and cell counts made as described below.

Immediately after BAL, the lung vasculature is flushed with RPMI 1640 / FCS to remove the blood pool of cells. The lung lobes are removed and cut into 0.5 mm pieces. Samples (rats: 400mg; mice: 150mg) of homogenous lung tissue are incubated in RPMI 1640 / FCS with collagenase (20 U/ml for 2 hours, then 60 U/ml for 1 hour, 37°C) to disaggregate cells from the tissue. Recovered cells are washed in RPMI 1640 / FCS.

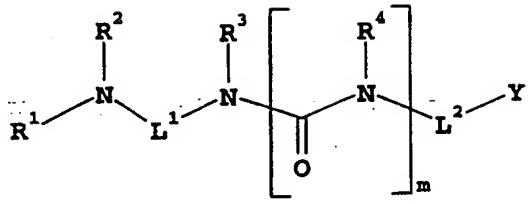
Counts of total leukocytes recovered from the airway lumen and the lung tissue are made with an automated cell counter (Cobas Argos, US). Differential counts of eosinophils, neutrophils and mononuclear cells are made by light microscopy of cytocentrifuge preparations stained with Wright-Giemza stain (Sigma, UK). T cells are counted by flow cytometry (EPICS XL, Coulter Electronics, US) using fluophore-labelled antibodies against CD2 (a pan-T cell marker used to quantify total T cells), CD4, CD8 and CD25 (a marker of activated T cells). All antibodies were supplied by Serotec Ltd., UK)

2.5 Data analysis.

The cell data was expressed as mean cell numbers in unchallenged, challenged and vehicle treated, and challenged and compound treated groups, including the standard error of the means. Statistical analysis of the difference among treatment groups was evaluated using one-way analysis of variance via the Mann-Whitney test. Where $p < 0.05$ no statistical significance existed. The inhibitors of the invention caused a statistically significant reduction in eosinophil and lymphocyte numbers in the BAL and airway tissue.

## CLAIMS

1. A compound of formula (I)



(I)

wherein:-

$R^1$ represents a group selected from :

(i) $R^5$-$L^3$-

(ii) $R^5$-$L^4$-$R^6$-

(iii) $R^5$-$L^4$-$R^7$-$L^5$-

(iv) $R^5$-$L^4$-$Ar^1$-$L^3$-

(v) $R^5$-$L^4$-$Ar^1$-$L^6$-$R^6$-

(vi) $R^5$-$L^4$-$Ar^1$-$R^7$-$L^5$-

$R^2$ represents hydrogen or lower alkyl;

$R^3$ and $R^4$ independently represent hydrogen or a group selected from alkyl, alkenyl and alkynyl each optionally substituted by one or more atoms or groups chosen from halo, oxo, $R^8$, -C(=O)-$R^9$, -NH-C(=O)-$R^9$ or -C(=O)$NY^1Y^2$; or

$R^3$ and $R^4$ together may represent -$(CH_2)_n$- or -C(=O)-CH=CH-;

$R^5$ is alkyl, alkenyl, alkynyl, aryl, arylalkyl, arylalkenyl, arylalkynyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkenyl, cycloalkylalkynyl, cycloalkenyl, cycloalkenylalkyl, heteroaryl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, heterocycloalkyl or heterocycloalkylalkyl;

$R^6$ is an alkylene chain;

$R^7$ is an alkylene chain, an alkenylene chain, or an alkynylene chain;

$R^8$ is an acidic functional group (or corresponding protected derivative), aryl, cycloalkyl, cycloalkenyl, heteroaryl, heterocycloalkyl, -$ZR^9$ or -$NY^1Y^2$;

$R^9$ is alkyl, aryl, arylalkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl or heterocycloalkylalkyl;

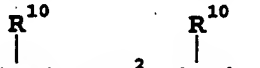
$R^{10}$ is a hydrogen atom or a lower alkyl group;

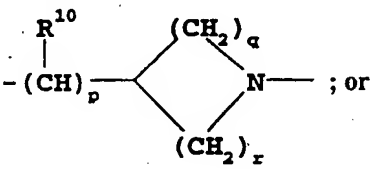
R is hydrogen or $R^9$;

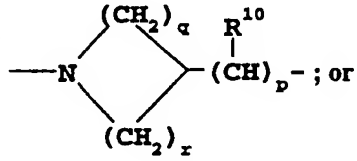
A is -N(R)- or -NH-C(=O)- ;

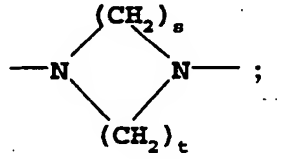
$Ar^1$ is phenylene or heteroaryldiyl;

$Ar^2$ is phenylene, cycloalkylene, heterocycloalkylene or heteroaryldiyl;

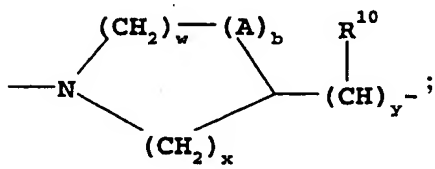
$L^1$ represents $C_{2-6}$alkylene or  ; or

the group -$L^1$-N($R^3$)- represents  ; or

the group -N($R^2$)-$L^1$- represents  ; or

the group -N($R^2$)-$L^1$-N($R^3$)- represents  ;

$L^2$ represents an alkylene, alkenylene, alkynylene, cycloalkenylene, cycloalkylene or heterocycloalkylene linkage, each optionally substituted by alkyl, alkenyl, alkynyl, aryl, carboxy (or an acid bioisostere), cyano, cycloalkenyl, cycloalkyl, heteroaryl, heterocycloalkyl, oxo, -C(=O)$R^9$, -C(=O)O$R^9$, -C(=O)N$Y^1Y^2$ or -N$Y^1Y^2$, or by alkyl substituted by aryl, carboxy (or an acid bioisostere), cyano, heteroaryl, heterocycloalkyl, hydroxy, mercapto, -C(=O)$R^9$, -C(=O)O$R^9$, -C(=O)N$Y^1Y^2$, -O$R^9$, S(O)$_V$$R^9$, -NHC(=O)OAlkyl, -N$Y^1Y^2$, -N$R^{10}$C(=Z)-N$Y^3Y^4$ or -NH-C(=NH)$NH_2$; or

the group -N($R^4$)-$L^2$- represents  ;

$L^3$ is a direct bond or a -C(=Z)-, -N$R^{10}$-C(=Z)-, -O-C(=O)-, -SO- or -$SO_2$- linkage;

$L^4$ represents a heteroaryldiyl, heterocycloalkylene, $-NR^{10}-C(=Z)-NR^{10}-$, $-C(=Z)-NR^{10}-$, $-C(=Z)-O-$, $-NR^{10}-C(=Z)-$, -Z-, -SO-, $-SO_2-$, $-NR^{10}-$, $-SO_2-NR^{10}-$, $-NR^{10}-SO_2-$, $-NR^{10}-C(=O)-O-$, $-O-C(=O)-$, or $-O-C(=O)-NR^{10}-$ linkage;

$L^5$ represents a $-C(=Z)-$, $-NR^{10}-C(=Z)-$, $-O-C(=O)-$, -SO- or $-SO_2-$ linkage;

$L^6$ is a direct bond, an alkenylene or alkynylene chain, or a -Z-, -SO-, $-SO_2-$, $-NR^{10}-$ linkage;

Y is carboxy (or an acid bioisostere) or $-C(=O)-NY^1Y^2$;

$Y^1$ and $Y^2$ are independently hydrogen, acyl, alkyl [optionally substituted by hydroxy, heterocycloalkyl, or one or more carboxy or $-C(=O)-NHR^9$ groups], alkylsulphonyl, aryl, arylalkyloxycarbonyl, arylsulphonyl, arylalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl or heterocycloalkylalkyl; or the group $-NY^1Y^2$ may form a 5-7 membered cyclic amine which (i) may be optionally substituted with one or more substituents selected from carboxamido, carboxy, hydroxy, oxo, hydroxyalkyl, $HOCH_2CH_2-(OCH_2CH_2)_v-$, or alkyl optionally substituted by carboxy or carboxamido (ii) may also contain a further heteroatom selected from O, S, $SO_2$ or $NY^5$ and (iii) may also be fused to additional aryl, heteroaryl, heterocycloalkyl or cycloalkyl rings to form a bicyclic or tricyclic ring system;

$Y^3$ and $Y^4$ are independently hydrogen, alkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl or heterocycloalkylalkyl;

$Y^5$ is hydrogen, alkyl, aryl, arylalkyl, $-C(=Z)R^9$ or $-SO_2R^9$;

Z represents an oxygen or sulphur atom;

b is zero or when w is at least 1 then b may also represent 1;

m is zero or 1;

n is an integer 2 to 4;

p is zero or an integer 1 to 3;

q is zero or an integer 1 to 4;

r is an integer 2 to 5; and

q+r is 2 to 7;

s is an integer 1 to 3;

t is an integer 2 or 3; and

s+t is 3 or 5;

v is 0, 1 or 2;

w is zero or an integer 1 to 3;

x is an integer 1 to 3; and

b+w+x is 1 to 5;

y is zero or an integer 1 to 3;

and their prodrugs, and pharmaceutically acceptable salts and solvates of such compounds and their prodrugs.

2. A compound according to claim 1 in which $R^1$ represents a group $R^5$-$L^4$-$Ar^1$-$L^3$- wherein $L^3$ is a -C(=O)- linkage, $Ar^1$ is optionally substituted phenylene or optionally substituted heteroaryldiyl, $L^4$ is a -NH-C(=O)-NH- linkage, and $R^5$ is an optionally substituted aryl group or an optionally substituted heteroaryl group.

3. A compound according to claim 1 in which $R^1$ represents a group $R^5$-$L^4$-$Ar^1$-$R^7$-$L^5$- wherein $L^5$ is a -C(=O)- linkage, $R^7$ is a straight or branched $C_{1-6}$alkylene chain, $Ar^1$ is optionally substituted phenylene or optionally substituted heteroaryldiyl, $L^4$ is a -NH-C(=O)-NH- linkage, and $R^5$ is an optionally substituted aryl group or an optionally substituted heteroaryl group.

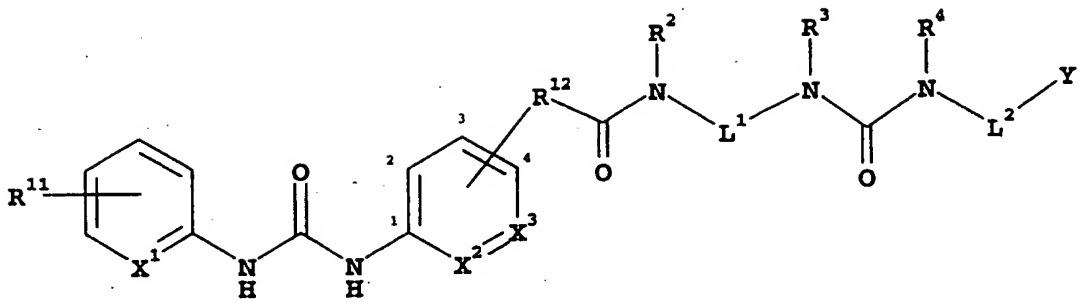
4. A compound according to any preceding claim in which $Ar^1$ is phenylene or pyridinediyl optionally substituted by $C_{1-4}$alkyl or $C_{1-4}$alkoxy.

5. A compound according to claim 4 in which $Ar^1$ is phenylene substituted by $C_{1-4}$alkyl or $C_{1-4}$alkoxy.

6. A compound according to any preceding claim in which $R^5$ is an optionally substituted phenyl group or an optionally substituted pyridyl group.

7. A compound according to claim 6 in which $R^5$ is a phenyl group substituted by $C_{1-4}$alkyl or $C_{1-4}$alkoxy.

8. A compound according to claim 1 having the formula (Ia)

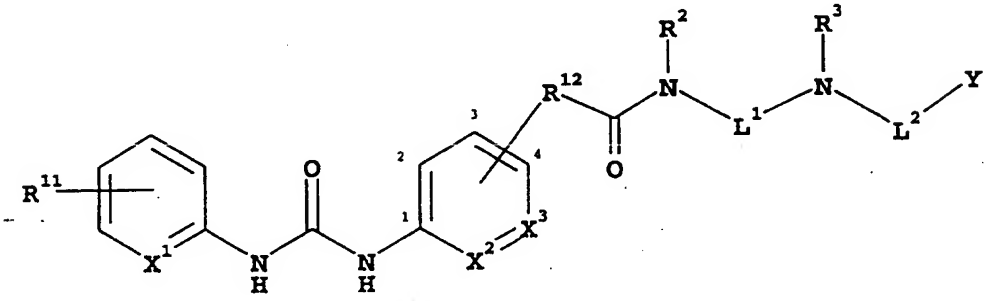


(Ia)

in which $R^2$, $R^3$, $R^4$, $L^1$, $L^2$ and Y are as defined in claim 1, $R^{11}$ is hydrogen, halogen, $C_{1-4}$alkyl or $C_{1-4}$alkoxy, $R^{12}$ is a direct bond or an alkylene chain, $X^1$, $X^2$ and $X^3$ independently represent N or $CR^{13}$ (where $R^{13}$ is hydrogen, halogen, $C_{1-4}$alkyl or $C_{1-4}$alkoxy), and $-R^{12}-C(=O)-N(R^2)-L^1-N(R^3)-C(=O)-N(R^4)-L^2-Y$ is attached at the ring 3 or 4 position, and their prodrugs and pharmaceutically acceptable salts, and solvates (e.g. hydrates) of compounds of formula (Ia) and their prodrugs.

9. A compound according to claim 8 in which the group $-R^{12}-C(=O)-N(R^2)-L^1-N(R^3)-C(=O)-N(R^4)-L^2-Y$ is attached at the ring 4 position.

10. A compound according to claim 1 having the formula (Ib):-



(Ib)

in which $R^2$, $R^3$, $L^1$, $L^2$ and Y are as defined in claim 1, $R^{11}$ is hydrogen, halogen, $C_{1-4}$alkyl or $C_{1-4}$alkoxy, $R^{12}$ is a direct bond or an alkylene chain, $X^1$, $X^2$ and $X^3$ independently represent N

or $CR^{13}$ (where $R^{13}$ is hydrogen, halogen, $C_{1-4}$alkyl or $C_{1-4}$alkoxy), and $-R^{12}-C(=O)-N(R^2)-L^1-N(R^3)-L^2-Y$ is attached at the ring 3 or 4 position, and their prodrugs and pharmaceutically acceptable salts, and solvates (e.g. hydrates) of compounds of formula (Ib) and their prodrugs.

11. A compound according to claim 10 in which the group $-R^{12}-C(=O)-N(R^2)-L^1-N(R^3)-L^2-Y$ may preferably be attached at the ring 4 position.

12. A compound according to any preceding claim in which $R^2$ represents hydrogen.

13. A compound according to any one of claims 1-11 in which $R^2$ represents methyl.

14. A compound according to any preceding claim in which $R^3$ represents hydrogen.

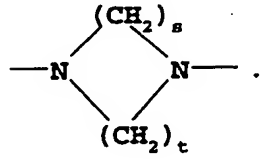
15. A compound according to any one of claims 1-13 in which $R^3$ represents methyl.

16. A compound according to any one of claims 1-9 and 12-15 in which $R^4$ represents hydrogen or $C_{1-4}$alkyl optionally substituted by aryl, heteroaryl, $-NY^1Y^2$, cycloalkyl, alkoxy or halo, or $R^4$ represents $C_{1-4}$alkenyl.

17. A compound according to any one of claims 1-9 and 12-15 in which $R^3$ and $R^4$ together represent -C(=O)-CH=CH-.

18. A compound according to any preceding claim in which $L^1$ represents a straight chain $C_{2-6}$alkylene.

19. A compound according to any one of claims 1-9 and 12-17 in which $L^1$ represents a $-Ar^2-$ linkage.

20. A compound according to any one of claims 1-17 in which the group $-N(R^2)-L^1-N(R^3)-$ represents  .

21. A compound according to any preceding claim in which $L^2$ represents a straight or branched $C_{1-4}$alkylene linkage.

22. A compound according to any one of claims 1-20 in which $L^2$ represents a straight or branched $C_{1-4}$alkylene linkage substituted by a group chosen from alkenyl, alkynyl, aryl, carboxy (or an acid bioisostere), cyano, cycloalkenyl, cycloalkyl, heteroaryl, heterocycloalkyl, $-C(=O)R^9$, $-C(=O)OR^9$, $-C(=O)NY^1Y^2$ or $-NY^1Y^2$, or by alkyl substituted by aryl, carboxy (or an acid bioisostere), cyano, heteroaryl, heterocycloalkyl, hydroxy, mercapto, $-C(=O)R^9$, $-C(=O)OR^9$, $-C(=O)NY^1Y^2$, $-OR^9$, $S(O)_vR^9$, -NHC(=O)OAlkyl, $-NY^1Y^2$, $-NR^{10}C(=Z)-NY^4Y^5$ or $-NH-C(=NH)NH_2$.

23. A compound according to any one of claims 8-22 in which $R^{11}$ represents hydrogen.

24. A compound according to any one of claims 8-23 in which $R^{12}$ represents a direct bond

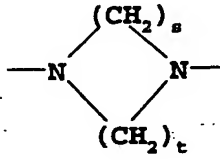
25. A compound according to any one of claims 8-23 in which $R^{12}$ represents methylene.

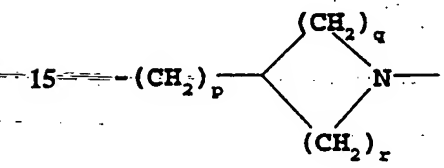
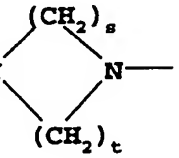
26. A compound according to any one of claims 8-25 in which $X^1$ represents $CR^{13}$, where $R^{13}$ is $C_{1-4}$alkyl or $C_{1-4}$alkoxy.

27. A compound according to any one of claims 8-26 in which $X^2$ represents $CR^{13}$, where $R^{13}$ is hydrogen or $C_{1-4}$alkoxy.

28. A compound according to any one of claims 8-27 in which $X^3$ represents CH.

29. A compound according to any preceding claim in which Y represents carboxy.

30. A compound according to claim 8 in which $R^2$ is hydrogen or $C_{1-4}$alkyl; $R^3$ is hydrogen or $C_{1-4}$alkyl; $R^4$ is hydrogen or $C_{1-4}$alkyl substituted by aryl or by $-NY^1Y^2$, or $R^3$ and $R^4$ together represent -C(=O)-CH=CH-; $L^1$ is a straight $C_{2-6}$alkylene chain or cycloalkylene; or the group $-N(R^2)-L^1-N(R^3)-$ represents  ; $L^2$ is a straight or branched $C_{1-4}$alkylene chain or a $C_{1-4}$alkylene chain substituted by $-C(=O)-NY^1Y^2$; $R^{11}$ is hydrogen; $R^{12}$ is a bond or a straight $C_{1-4}$alkylene chain; $X^1$ represents C-methyl; $X^2$ represents C-methoxy; $X^3$ represents CH; Y represents carboxy; and the group $-R^{12}-C(=O)-N(R^2)-L^1-N(R^3)-C(=O)-N(R^4)-L^2-Y$ is attached at the ring 4 position; and their prodrugs, and pharmaceutically acceptable salts and solvates of such compounds and their prodrugs.

31. A compound according to claim 10 in which $R^2$ is hydrogen; $R^3$ is hydrogen or $C_{1-4}$alkyl; $L^1$ is a straight $C_{2-6}$alkylene chain; or the group $-L^1-N(R^3)-$ represents  where p is 0 or 1 and q+r is 3 or 4); or the group $-N(R^2)-L^1-N(R^3)-$ represents  ; $L^2$ is a straight or branched $C_{1-4}$alkylene chain or a $C_{1-4}$alkylene chain substituted by oxo or by $-C(=O)-NY^1Y^2$; $R^{11}$ is hydrogen; $R^{12}$ is a straight $C_{1-4}$alkylene chain; $X^1$ represents C-methyl; $X^2$ represents C-methoxy; $X^3$ represents CH; Y represents carboxy; and the group $-R^{12}-C(=O)-N(R^2)-L^1-N(R^3)-L^2-Y$ is attached at the ring 4 position; and their prodrugs, and pharmaceutically acceptable salts and solvates of such compounds and their prodrugs.

32. A pharmaceutical composition comprising an effective amount of a compound according to claim 1 or a corresponding prodrug, or a pharmaceutically acceptable salt or solvate of such a

compound or a prodrug thereof, in association with a pharmaceutically acceptable carrier or excipient.

33. A compound according to claim 1 or a corresponding prodrug, or a pharmaceutically acceptable salt or solvate of such a compound or a prodrug thereof, for use in therapy.

34. A compound according to claim 1 or a corresponding or a corresponding prodrug, or a pharmaceutically acceptable salt or solvate of such a compound or a prodrug thereof, for use in the treatment of a patient suffering from, or subject to, conditions which can be ameliorated by the administration of an inhibitor of $\alpha 4\beta 1$ mediated cell adhesion.

35. A composition according to claim 34 for use in the treatment of a patient suffering from, or subject to, conditions which can be ameliorated by the administration of an inhibitor of $\alpha 4\beta 1$ mediated cell adhesion.

36. A compound or composition according to claim 1 or 35 respectively for use in the treatment of inflammatory diseases.

37. A compound or composition according to claim 1 or 35 respectively for use in the treatment of asthma.

38. Use of a compound according to claim 1 or a corresponding prodrug, or a pharmaceutically acceptable salt or solvate of such a compound or a prodrug thereof, in the manufacture of a medicament for the treatment of a patient suffering from, or subject to, conditions which can be ameliorated by the administration of an inhibitor of $\alpha 4\beta 1$ mediated cell adhesion.

39. Use of a compound according to claim 1 or a corresponding prodrug, or a pharmaceutically acceptable salt or solvate of such a compound or a prodrug thereof, in the manufacture of a medicament for the treatment of asthma.

40. A method for the treatment of a human or non-human animal patient suffering from, or subject to, conditions which can be ameliorated by the administration of an inhibitor of $\alpha 4\beta 1$ mediated cell adhesion comprising administering to said patient an effective amount of a

compound according to claim 1 or a corresponding prodrug, or a pharmaceutically acceptable salt or solvate of such a compound or a prodrug thereof.

41. A compound as substantially hereinbefore described with references to the Examples.

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# INTERNATIONAL SEARCH REPORT

Inter. nal Application No
PCT/GB 99/01230

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D295/182 A61K31/17 A61K31/41 C07C275/42

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07C C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| E | WO 99 23063 A (RHONE-POULENC RORER LIMITED) 14 May 1999 (1999-05-14) claims 1,26,54 | 30,38 |
| A | WO 97 36862 A (G.D. SEARLE & CO.) 9 October 1997 (1997-10-09) claim 1 | 30 |
| A | WO 97 03094 A (BIOGEN, INC.) 30 January 1997 (1997-01-30) claim 1 | 30 |

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 16 August 1999 | 23/08/1999 |

| Name and mailing address of the ISA | Authorized officer |
|---|---|
| European Patent Office, P.B. 5818 Patentlaan 2<br>NL - 2280 HV Rijswijk<br>Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,<br>Fax: (+31-70) 340-3016 | Kapteyn, H |

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB 99/01230

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-29 partially, 32-41 partially

Present claims 1-29 relate to an extremely large number of possible compounds. In fact, the claims contain so many options, variables, possible permutations, that a lack of clarity and conciseness within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of the claims impossible. In addition the definition R1 in claim 1 does not correspond with at least a part of the compounds claimed with the formulas 1a and 1b of the claims 8 and 10, which are dependend from claim 1.

Consequently, the search has been carried out for those parts of the application which do appear to be clear and concise, namely claims 30 and 31 and claims 32-41 partially.

Therefor the search has been executed for compounds with the following definitions for the variables of formulas 1a and 1b acording to the claims 30 and 31:

R3 = hydrogen or C1-4 alkyl
R4 = hydrogen or C1-4 alky substituted by aryl or by -NY1Y2
or R3 and R4 = -C(=O=)-CH=CH-
L1 = straight C2-6 alkylene chain or cycloalkylene
or -N(r2)-L1-N(R3)- = definition given in claim 30 at line 5
or -L1-N(R3)- = definition given in claim 31 at line 15
L2 = straight or branched C1-4 alkylene chain or a C1-4 alkylene chain substituted by -C(=O)-NY1Y2
R11 = hydrogen
R12 = bond or a straight C1-4 alkylene chain
X1 = C-methyl
X2 = C-methoxy
X3 = CH
Y = carboxy
the group containing R12 is attached at the ring position 4

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

# INTERNATIONAL SEARCH REPORT

information on patent family members

Inter ·nal Application No
PCT/GB 99/01230

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---|---|---|
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| | | EP 0889877 A | 13-01-1999 |
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| | | PL 324491 A | 25-05-1998 |
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